ASSESSMENT OF MAGNETIC RESONANCE IMAGING AND POSITRON EMISSION TOMOGRAPHY-DERIVED NEURODEGENERATIVE AND CEREBROVASCULAR MARKERS OF ALZHEIMER'S DISEASE

Thesis (cumulative thesis)
Presented to the Faculty of Arts and Social Sciences
of the
University of Zurich
For the Degree of Doctor of Philosophy

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Zurich, 2016

“How old would you be if you didn't know how old you were?”

(Satchel Paige)

Table of Contents

1 Acknowledgements

I am pleased to present this cumulative dissertation on cerebrovascular markers in cognitive aging and Alzheimer's disease, bridging reflections on healthy aging, current pathological and clinical definitions of Alzheimer's disease, and cerebrovascular risk markers commonly observed in aging.

This dissertation has been a collaborative and international effort, and my gratitude goes to all who have supported me over the course of my PhD, although only a few can be named here.

First and foremost, I would like to express my highest appreciation to Dr. Adam Brickman (CUMC), my mentor of seven years, who accompanied me near and far since the very beginning and sparked this entire process of my scientific growth, who simultaneously challenged and supported me, served as a research mentor and clinical supervisor, introduced me to the world of science and academia, facilitated collaborations, provided data, guided me through grant applications and doctoral research, taught me how to speak at conferences and how to set up research studies, how to analyze data, write papers, and review articles, how to lead a group and how to motivate students, who trusted me with his own work and always took me seriously, who gave me my required freedom yet necessary encouragement, never judged for alternative ideas nor shied at additional work load, who always put his students needs before his own ones, and who was always available for advice and tireless in answering questions. You were the perfect role model in all these aspects and it is needless to say that this dissertation and my continuance in academia would not exist without your inspiring enthusiasm, motivation, commitment, drive, and effort over all these years.

Similarly, I would like to thank my doctoral advisor Prof. Christoph Hock (UZH) for his flexibility, openness and encouragement of a collaborative PhD, for his availability and advice throughout, for his time and resourcefulness, motivating words, critical questions, trust and freedom, support in acquiring independent funding, and for allocating me to an excellent mentor: Dr. Paul Unschuld (UZH), who offered me data for analysis, accompanied me at scientific conferences, responded to emails within minutes, and was tireless in supporting manuscript submissions. Thank you for your detailed imaging and statistical knowledge and according suggestions for research papers, careful corrections and feedback, circulation of relevant research papers, and accommodating national and international meetings.

Another great thank you goes out to the Profs. Klaas Pruessmann (ETHZ), and in particular Mike Martin (UZH), for waking my interest in geriatric topics in the first place, for co-examining this dissertation, and for the organization of the final exam.

I would like to express great thanks to Daniel Summermatter from the Division of Psychiatry Research for his introduction into clinical neuropsychology seven years ago, as well as acquisition of data, and thank all of the staff from both locations and study subjects for participating and contributing to meaningful science. Thank you to Dr. Andrea Kälin for study materials, guidance, and supporting words in the most critical phases, and to Dr. Anton Gietl for his outstanding knowledge about his study samples, careful feedback, his time, logical contemplations, and his considerate and calm way of being.

Furthermore, my gratitude goes to Dr. Daniel Halter (ETHZ) for a decade of scientific and career-advice and circulating papers, and for enthusiastically supporting any of my projects, and to Prof. Lawrence Rajendran for stimulating scientific discussions and his valued feedback, emotional support, hilarious jokes, brilliant ideas, and motivational words. Also thank you to swissnex Brazil – for their patience to introduce me into the world of diplomacy, for the freedom and creativity in project management, the insight into entrepreneurship, as well as the support during my dissertation, and for laying a foundation for future endeavors and sparking new ideas in merging the academic and entrepreneurial worlds.

Lastly, I would like to thank my friends and family, who could not be happier about my privileged situation, who supported me where necessary and scolded me when needed, and who spoiled me in laborious phases and exam periods, while an additional particular thank you goes to my parents for their stimulating environment and giving me the opportunity to study in the first place.

2 Abstracts

This dissertation will elaborate the importance of vascular risk in the ethiology of Alzheimer's disease (AD). We showed that presence of two or more microbleeds, a marker of cerebral amyloid angiopathy (CAA), is associated with a faster decline in executive functioning over time than less than two microbleeds (β =-.072; p=0.012). Further, we showed that the presence of microbleeds is associated with poorer performance on an executive functioning test than absence of microbleeds (t=2.449; p=0.029), demonstrating that high resolution 7T MRI is a useful tool to detect microbleeds. We also showed greater WMH burden (a second marker for small vessel disease) in frontal and parietal lobes (F(3, 519)=9.82; p<0.001), and a bigger increase of total WMH volume over time (F(1, 173)=9.61; p<0.05) in subjects with microbleeds over those without lobar microbleeds, suggesting that the two markers reflect the same underlying pathology. Lastly, using SPECT and PET data, we showed that areas with highest normative blood perfusion in the young subjects display highest values of amyloid deposition in older adults (F(3,27)=3.19; p=0.036), suggesting that areas with relatively high blood perfusion in young adulthood are more susceptible to amyloid deposition in late life. The findings consistently cover the contribution of regional vascular damage in the pathogenesis of AD and point at important early vascular markers that may have implications for treatment and preventative interventions in AD.

Das Ziel dieser Dissertation war, die Rolle cerebrovaskulärer Marker bei der Pathogenese der Alzheimer Krankheit (AK) zu untersuchen. Wir zeigten, dass das Vorliegen von Mikroblutungen, ein Marker von Amyloidangiopathie, assoziiert war mit einer signifikant schnelleren Abnahme von Exekutivfunktionen im Verlauf, Amyloidangiopathie also ein wichtiger Marker im Kontext des kognitiven Alters sein könnte. Ausserdem konnten wir belegen, dass die hochauflösende 7Tesla-MRI-Bildgebung ein brauchbares Instrument zum Nachweis von Mikroblutungen ist. Teilnehmer mit Mikroblutungen zeigten zudem signifikant mehr T2-Hyperintensitäten in frontalen und parietalen Hirnregionen und eine Zunahme in allen Regionen über 10 Jahre hinweg als Teilnehmer ohne Mikroblutungen, was eine gemeinsame Pathologie annehmen könnte. Auch zeigten wir, dass Regionen mit der stärksten Durchblutung bei jungen Teilnehmern die höchste Anhäufung von Amyloid bei älteren Erwachsenen aufwiesen, diese Regionen also im späteren Leben anfälliger für die Ablagerung von Amyloid sein könnten. Unsere Resultate heben somit die Bedeutung früher regionaler vaskulärer Veränderungen bzw. Einflüsse hervor und unterstützen die Annahme, dass diesen eine wichtige Rolle bei der Frühdiagnostik sowie der Therapie der AK zukommen könnte.

3 Summary/Zusammenfassung

Summary

Alzheimer's disease (AD) is the most common cause of dementia. Models of AD pathogenesis have focused primarily on amyloid-related mechanisms as primary instigators of the disease. Recent literature, however, highlights the importance of vascular factors in the etiology of AD; hypertension, diabetes, insulin resistance, obesity, and hyperlipidemia all affect onset and risk of developing AD, severity of symptoms and/or speed of disease progression, and rate of cognitive decline. The overall purpose of the four experiments that comprise this dissertation was to examine systematically the contributions of markers of cerebrovascular disease to AD pathogenesis and cognitive aging, using neuroimaging in human studies of cognitive aging.

The first study examined the relationship between lobar cerebral microbleeds, a marker of cerebral amyloid angiopathy (CAA), quantified on T2* gradient echo (GRE) MRI sequences, and longitudinal change in executive functioning in 197 older subjects without dementia from an ongoing community-based study of cognitive aging and dementia. The results of a general estimating equation (GEE) showed that presence of two or more microbleeds is associated with a faster decline in executive functioning over time than less than two microbleeds (β =-.072; p=0.012). Hence, the presence of amyloid angiopathy may be an important predictor of cognitive decline in aging.

For our second study, we used 7T MRI scans to examine the relationship between lobar microbleeds and cognition in a small group of relatively young, healthy older adults (over age 55; mean = 68.27 +/-5.15). Five out of the 15 subjects had lobar microbleeds. T-tests comparing the two groups showed that presence of microbleeds is associated with poorer performance on an executive functioning test than absence of microbleeds (t=2.449; p=0.029), confirming the association between microbleeds and executive functioning from study one. The finding further demonstrates that, besides the higher signal-to-noise-ratio, high resolution 7T MRI is a useful tool to detect microbleeds.

The third study aimed to establish the relationship between microbleeds and the accumulation of regional white matter hyperintensities (WMH), another measure of small vessel cerebrovascular disease. Thirty-nine out of 187 subjects from an ongoing community-based study had lobar

microbleeds, and showed greater WMH burden in frontal and parietal lobes ($F(3, 519)=9.82$; $p<0.001$), and a bigger increase of total WMH volume over time ($F(1, 173)=9.61$; $p<0.05$) than subjects without lobar microbleeds, suggesting that the two representations of small vessel disease may in fact reflect the same underlying pathology and/or have a degree of codependency and contribute to the onset of cognitive decline.

The final experiment examined the extent to which normative cerebral perfusion is associated spatially with amyloid deposition in older adults. Normative SPECT data were derived from an open access atlas of young (age 22-49), healthy adults, which was spatially compared to the distribution of amyloid deposition in 128 older adults. The results showed that areas with highest normative blood perfusion in the young subjects display highest values of amyloid deposition in older adults ($F(3,27)=3.19$; $p=0.036$). Findings suggest that areas with relatively high blood perfusion in young adulthood are more susceptible to amyloid deposition in late life.

Taken together, we showed that markers of vascular disease in healthy older adults contribute to cognitive decline, that high field strength imaging is a useful tool for the detection of such markers, and that normative perfusion is spatially related to increased AD pathology later in life. The findings consistently cover the contribution of regional vascular damage or vascular regulations in the pathogenesis of Alzheimer's disease and point at important early vascular markers that may have implications for treatment and preventative interventions in AD.

We speculate ways in which vascular factors and AD pathology might interact, discuss why previous vascular treatments have not been successful interventions to date, and suggest, based on our findings, that vascular markers be considered in diagnostic and prognostic formulations in the clinic, as well as in research related to AD pathogenesis and progression.

Zusammenfassung

Die Alzheimer-Krankheit (AK) ist mit Abstand die häufigste Demenzform des höheren Lebensalters und hat in den letzten Jahren sowohl in Gesellschaft als auch in der Forschung zunehmend an Bedeutung gewonnen. Modelle zur Pathogenese der AK haben sich in den letzten 20 Jahre vorwiegend auf Amyloid-assoziierte Mechanismen fokussiert. Neuere Forschungen deuten allerdings auch auf einen hohen Stellenwert vaskulärer Risikofaktoren bei der AK-Pathogenese hin: Bluthochdruck, Diabetes, Insulinresistenz, Übergewicht sowie Fettleibigkeit üben allesamt einen Einfluss sowohl auf den Beginn als auch den klinischen Verlauf der AK, den Ausprägungs- und Schweregrad der Krankheitssymptome und/oder die Geschwindigkeit des Krankheitsverlaufs auf, und tragen somit entscheidend zum kognitiven Leistungsabbau bei. Das Ziel der in dieser Dissertation dargestellten vier Experimente war es, die Rolle spezifischer bildgebender cerebrovaskulärer Marker bei der AK-Pathogenese und bei kognitiven Alterungsprozessen systematisch zu beleuchten. Hierbei kamen verschieden Methoden der cerebralen Bildgebung bei Studienprobanden zum Einsatz, die in verschiedenen Studien zum kognitiven Altern untersucht wurden

Die erste Studie untersuchte den Zusammenhang zwischen lobären cerebralen Mikroblutungen, einem Marker der cerebralen Amyloidangiopathie (CAA), dargestellt mittels T2*-gewichteten Gradient Echo (GRE) MRI-Sequenz, und Veränderungen exekutiver Teilfunktionen in neuropsychologischen Testverfahren über einen Zeitraum von knapp zehn Jahren. Untersucht wurden insgesamt 197 nicht-demente ältere Studienteilnehmer einer fortlaufenden, gemeinschaftsbasierten Studie über kognitives Altern und Demenz. Auswertungen von Regressionsanalysen (GEE) ergaben dabei, dass das Vorliegen von Mikroblutungen – im Gegensatz zum Nichtvorhandensein von Mikroblutungen – assoziiert war mit einer signifikant schnelleren Abnahme von Exekutivfunktionen im Verlauf (β=-.072; p=.012). Die beiden Gruppen unterschieden sich dabei voneinander nicht hinsichtlich des Alters, der ethnischen Zugehörigkeit, der Geschlechterverteilung bzw. der kognitiven Leistungsfähigkeit bei der ersten Untersuchung. Diese Resultate implizieren folglich, dass das Vorhandensein der Amyloidangiopathie ein wichtiger Marker im Kontext des kognitiven Alters sein könnte.

Im Rahmen der zweiten Studie wurden 7Tesla-MRI-Aufnahmen herangezogen, um den Zusammenhang zwischen Mikroblutungen und kognitiver Leistungsfähigkeit in einer kleinen Gruppe von gesunden älteren Erwachsenen (55 Jahre und älter) zu untersuchen. Fünf von 15 Teilnehmern wiesen hierbei lobäre Mikroblutungen auf. Mittels t-Tests verglichen wir die beiden Gruppen (Probanden mit und ohne Mikrobulutungen), und konnten bei Teilnehmern mit

Mikroblutungen eine geringere Leistung in Tests zu exekutiven Teilfunktionen objektivieren ($t=2.449$; $p=0.029$), was mit den Resultaten aus der ersten Studie gut vereinbar ist. Zudem konnte diese Studie belegen, dass die hochauflösende 7Tesla-MRI-Bildgebung - trotz eines insgesamt höheren Signal-Rausch-Verhältnisses - ein brauchbares und nützliches Instrument zum Nachweis von Mikroblutungen darstellt.

Die dritte Studie erbrachte den Nachweis über den Zusammenhang von cerebralen Mikroblutungen und regional verteilten T2-Hyperintensitäten der weissen Substanz, einem weiteren cerebrovaskulären Marker, der insbesondere eine Schädigung kleinerer cerebraler Gefässe abbildet. Neununddreissig von 187 Teilnehmer der gleichen Studie wie in Experiment 1 wiesen lobäre Mikroblutungen auf und zeigten signifikant mehr T2-Hyperintensitäten in frontalen und parietalen Hirnregionen ($F(3, 519)=9.82$; $p<0.001$) und eine Zunahme in allen Regionen über 10 Jahre hinweg ($F(1, 173)=9.61$; $p<0.05$) als Teilnehmer ohne Mikroblutungen. Diese Ergebnisse deuten darauf hin, dass beiden cerebrovaskulären Markern (d.h. sowohl den Mikroblutungen als auch den T2-Hyperintensitäten) möglicherweise eine gemeinsame Pathologie zugrunde liegen könnte, und dass beide Marker zum kognitiven Leistungsabfall beitragen.

Das letzte Experiment untersuchte schliesslich, in welchem Ausmass die regional verteilte normative Hirndurchblutung zur Ablagerung von Amyloid bei älteren Erwachsenen beiträgt. Normative SPECT-Daten stammten von einem öffentlich zugänglichen Hirnatlas von jungen, gesunden Erwachsenen (22-49jährig) und wurden für die Untersuchung der regionalen Durchblutung herangezogen, die zur Ablagerung von Amyloid bei 128 älteren Erwachsenen räumlich in Beziehung gesetzt wurde. Unsere Auswertungen zeigten, dass jene Regionen mit der stärksten Durchblutung bei jungen Teilnehmern die höchste Anhäufung von Amyloid bei älteren Erwachsenen aufwiesen ($F(3,27)=3.19$; $p=0.036$). Diese Ergebnisse sind vereinbar mit der Annahme, dass Hirnregionen mit über die Lebensspanne hinweg relativ erhöhter Durchblutung im späteren Leben anfälliger für die Ablagerung von Amyloid sein könnten.

Zusammengefasst konnten wir im Rahmen dieser Dissertation nachweisen, dass spezifische bildgebende cerebrovaskuläre Marker bei gesunden älteren Menschen zur kognitiven Leistungsabnahme beitragen, und dass hochauflösende MRI-Bildgebung ein nützliches Instrument bei der Detektion dieser Marker darstellen kann. Darüber hinaus konnten wir im Rahmen unserer Forschungen zeigen, dass normativer cerebraler Blutfluss räumlich in Beziehung gesetzt werden kann zum Auftreten der Amyloid-Pathologie im späteren Leben. Unsere Resultate heben somit die

Bedeutung früher regionaler vaskulärer Veränderungen bzw. Einflüsse hervor und unterstützen die Annahme, dass diesen eine wichtige Rolle bei der Frühdiagnostik sowie der Therapie der AK zukommen könnte.

In unserer Diskussion stellten wir abschliessend umfangreiche Überlegungen zur hypothetischen Beziehung zwischen vaskulären Faktoren und der „klassischen" AK-Pathologie an. Hierbei gingen wir unter anderem auch der Frage nach, was die Gründe für das Scheitern früherer vaskulär-basierter Therapieverfahren der AK gewesen sein könnten. Aufbauend auf den Ergebnissen dieser Dissertation schlugen wir vor, dass vaskuläre Marker in Zukunft sowohl in der AK-Diagnostik als auch bei prognostischen Überlegungen im klinischen Setting mehr Berücksichtigung finden sollten. In der Grundlagenforschung sollte darüber hinaus ein besonderes Augenmerk auf vaskuläre Faktoren im Kontext der Krankheitsentstehung und der Krankheitsprogression geworfen werden.

4 Introduction

With the growth of the aging population, there is an international increase in the prevalence of dementia, but no cure or treatment other than suboptimal symptomatic relief is currently available. Alzheimer's disease (AD) is the most common cause of dementia and is pathologically defined as presence of senile plaques (beta-amyloid) and neurofibrillary tangles (abnormally phosphorylated tau) (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011). It is a disabling neurodegenerative disorder characterized by progressive memory decline and loss of other cognitive functions that ultimately impede independent living.

After years of investigation into the biology of AD and major advances in biomarker research, research diagnostic criteria have been recently revised to define *clinical* AD and its ostensible antecedent conditions, all of which include biomarkers (C. R. Jack, Jr., 2011). *Preclinical AD* is defined as presence of at least Aβ before clinical symptoms of disease appear (Sperling, Aisen, et al., 2011). *Mild Cognitive Impairment (MCI) due to AD* is defined as subjective complaint in cognition, with impairment in one or more cognitive domains, while functional abilities are preserved, in addition to evidence of Aβ, tau deposition, or signs of neuronal injury (Albert et al., 2011). Finally, *dementia due to AD* is defined as cognitive and behavioral symptoms that affect functional activities with gradual onset of symptoms and decline of previous levels of performance involving at least two of five neuropsychological domains (memory, executive functions, language, visuospatial abilities, and personality) (McKhann et al., 2011), plus presence of the biomarkers amyloid and downstream neuronal degeneration or injury.

Despite these well-defined diagnostic criteria, which emphasize amyloid, tau, and neurodegenerative biomarkers, emerging literature indicates a strong involvement of vascular risk factors and markers in onset and risk of developing AD (Breteler, 2000; Decarli, 2004) as well as in the severity of symptoms (Snowdon et al., 1997), suggesting that the current diagnostic criteria for AD are incomplete.

Major advances in neuroimaging have allowed the operational definition and in vivo measurement of many markers associated with AD pathology. Magnetic resonance imaging has opened a window into the pathophysiology of AD, revealing spatial and temporal evolution of progressive brain changes and can serve as a diagnostic aid in distinguishing AD from other causes of dementia

and age-related changes in cerebral structure. It has been shown to be particularly useful in the appreciation neurodegeneration through cortical thickness and volume measures, cerebral blood flow changes, as well as cerebrovascular health, such as small and large vessel disease, that seem to add additional information helpful to understand changes that may predict clinical outcomes, disease presentation, and to monitor conversion and progression over time. Hence, structural MRI (For example, see Chapter 10.1) represents a key imaging marker for the early detection of AD.

The second routinely used imaging modality in AD research and clinical diagnosis is positron emission tomography (PET). Radioligands that bind to fibrillar forms of amyloid were introduced within the last decade and have, for the first time, allowed for the visualization of primary AD pathology in vivo (Johnson, Fox, Sperling, & Klunk, 2012). Several amyloid PET tracers are currently available and have received FDA approval in the US to assist in the diagnosis of AD. From a clinical perspective, a positive amyloid PET scan does not establish a definitive diagnosis but, following current diagnostic conventions, a negative amyloid PET scan makes a diagnosis of AD unlikely among symptomatic individuals.

From a research perspective, these modalities allow us to examine the inter-relationship among various hypothesized features of the disease, such as small vessel disease and distribution of pathology. Given the emerging evidence that links vascular risk to AD presentation and progression, we aimed to examine imaging parameters visualizing microbleeds, white matter hyperintensities, amyloid, and blood flow. These data were considered in the context of neuropsychological test performance to improve our understanding of aberrant changes in the aging brain and elucidate their effects on cognition. While much work involving neuroimaging studies of cognitive aging and dementia focuses on the development and validation of biomarkers, our approach seeks to use neuroimaging to help clarify what the neurobiological underpinnings are that mediate cognitive aging and dementia. From a public health perspective, being able to detect such markers in healthy older adults would allow for the conceptualization and implementation of preventive strategies, with the goal of decreasing the risk of dementia and maximizing healthy cognitive aging.

Chapter 7.2 will outline the cognitive tests used for the neuropsychological assessment in the current experiments. While memory effects may be more salient clinically and subjectively, and typically characteristic for AD, vascular risk factors are mostly known to impair executive functions (EF) (Nishtala et al., 2014), a diverse set of higher order skills that enable complex, goal-directed

behavior, set shifting, inhibition, fluency, problem solving, abstract reasoning, and strategy generation (Cosentino, 2011), which interact with memory effects (Buckner, 2004; Kirova, Bays, & Lagalwar, 2015; Parks et al., 2011). Besides, changes in executive functioning may be detectable earlier due to more sensitive tests, which is why they will be the main focus in our studies.

After this introduction, Chapter 5 will provide background information on Alzheimer's pathology, cover the area of healthy aging, and go more in depth on vascular contributors to Alzheimer's disease. Vascular risk factors will be discussed, as well as different cerebrovascular markers such as white matter hyperintensities (WMH) and microbleeds. Chapter 6 will outline the specific aims and research questions, Chapter 7 will specify methodological details on subjects, neuropsychological assessment, and imaging approaches used in the studies, followed by empirical data to support the hypotheses (Chapter 8). Finally, Chapter 9 will summarize and discuss the results and comment on future directions.

5 Theoretical background

5.1 Alzheimer's disease pathology and definition

Alzheimer's disease is pathologically defined as presence of extracellular senile plaques (Aβ; amyloid beta peptides) and intracellular neurofibrillary tangles (abnormally phosphorylated tau) (Hanft, Komotar, Raper, Sisti, & McKhann, 2011; Serrano-Pozo et al., 2011). Hyperphosphorylated tau is thought to impair axonal transport, leading to intraneuronal aggregation, as well as synaptic dysfunction and neuronal death (Walker, Diamond, Duff, & Hyman, 2013). Tau formation and atrophy, appreciated via neuroimaging or on gross examination of postmortem tissue, follow a similar spatial pattern (Tondelli et al., 2012; Whitwell et al., 2012), beginning with perirhinal and entorhinal cortices, CA1/subiculum field of the hippocampal formation and other mediotemporal regions, amygdala, and neocortex (Arriagada, Marzloff, & Hyman, 1992; Braak & Braak, 1991). Aβ starts clustering in the basal neocortex and expands to the striatum and cholinergic nuclei of the basal forebrain (Braak & Braak, 1991; Thal, Rub, Orantes, & Braak, 2002), while hippocampal regions are relatively spared until later in the process (Braak & Braak, 1991).

Reflected in the pathological (Montine et al., 2012) and clinical criteria for AD (McKhann et al., 2011) is the prevailing hypothesis that the clinical syndrome of AD is due to a unitary cascade of biological events that begins with the deposition of beta amyloid, which leads to tau aggregation/neurofibrillary tangles, causing neurodegeneration and associated cognitive and ultimately functional decline (Hardy & Selkoe, 2002). The described temporal and spatial separation of neurofibrillary tangles and Aβ aggregation has led to conclude that the two pathologies may not be causally interconnected (Reitz, 2012). In fact, recent research on AD-related tau pathology suggests that brainstem nuclei state the beginning of tau pathology, from where its spread takes an upward course towards the allocortex and further on, in line with the Braak stages (Stratmann et al., 2016), preceding amyloid presence and inconsistent with the amyloid hypothesis that suggests a necessary and precipitating role of amyloid pathology. Supporting evidence comes from the AD biomarker model, including the possibility of tau pathology before Aβ plaques (Braak & Braak, 1997a) in its revised version (C. R. Jack et al., 2013).

Furthermore, several lines of investigation implicate other pathological phenomena in the clinical presentation of AD, and possibly, in disease pathogenesis. Recent observations such as studies

showing amyloid negativity in clinically diagnosed AD (Landau, Horng, Fero, Jagust, & Alzheimer's Disease Neuroimaging, 2016), and the consistent observation that up to 30% of older adults with amyloid show no cognitive impairment whatsoever (Torre, 2004; Jack et al., 2008; Mintun et al., 2006; Provenzano et al., 2013), are not exactly incompatible since the definition of AD is unfortunately set up in an unfalsifiable manner (e.g., dementia will manifest in the future among asymptomatic individuals with amyloid unless they expire first), but are definitely not in favor of and entirely coherent with the current criteria of AD, thus hinting at a conceptual error in the formulation of the definition.

Probably the most compelling evidence that the amyloid hypothesis is incomplete comes from the repeated observation that vascular factors increase risk for and accelerate progression of AD. Up to 84% of aged subjects show morphological changes consistent with cerebrovascular disease in addition to classical AD pathology (Attems & Jellinger, 2014). Furthermore, vascular risk factors such as hypertension, diabetes, insulin resistance, obesity, and hyperlipidemia are associated with cognitive decline and dementia (Breteler, 2000; DeCarli et al., 2001; Gootjes et al., 2004; Helzner et al., 2009; Kivipelto et al., 2001; D. Knopman et al., 2001; Roher et al., 2003) in older age as well as when vascular factors are diagnosed in midlife (Nishtala et al., 2014). These risk factors are shared by both, Alzheimer's disease and vascular dementia (de la Torre, 2002), with vascular dementia having a more sudden onset of cognitive symptoms than the gradual beginning of symptoms observed in AD. Honig and colleagues (Honig, Kukull, & Mayeux, 2005), among others (Greiner, Snowdon, & Greiner, 1999; Vermeer et al., 2003) showed that in addition to these risk factors, cerebral infarcts are associated with higher risk and/or earlier onset of AD, and strongest in the presence of vascular risk factors, suggesting additive or synergistic effects of cerebrovascular damage in the presence of AD pathology. That is, A) Vascular disease is additively contributing to the phenotype of AD, but not to the pathology. B) Vascular disease interacts with AD pathology, such that AD pathology has a stronger impact in the context of vascular disease or vascular disease promotes cognitive impairment more so in the context of AD than without. Or C) Vascular disease is causally related to AD pathology. Option D), that both vascular and AD pathology act as a second hit as a result of a first, unknown process that we currently overlook, is another feasible possibility, but will not be discussed here.

Yet, in order to be able to define and study pathology and 'abnormal' aging, we first require a conceptualization of healthy, normal aging and an operational definition of what distinguishes normal from pathological aging.

5.2 Healthy aging and 'gray areas'

In Greek Mythology, Oedipus Rex was the first one to solve the Riddle of the Sphinx and knew that the answer to "What walks on four legs in the morning, two legs in the afternoon, and three legs in the evening?" was "a man". As a baby, he goes about on all fours, as an adult on two, until old age requires him to use a cane to support himself. In other words, the classical belief that aging is defined by a loss of function is indeed very old (Hummert, Garstka, Shaner, & Strahm, 1994; Lineweaver T. & Hertzog, 1998). Contemporary research, however, has taught us that despite increasing age, certain aspects of the human condition stay stable or even improve, such as social-emotional regulation, adaptivity, plasticity, expertise, and compensation (Baltes, 1990; K. W. C. Schaie, L.L., 2006).

Similarly, verbal abilities as well as information and comprehension tend to show stability (Kramer, Bherer, Colcombe, Dong, & Greenough, 2004), while vocabulary and other word-related language skills as well as fluid reasoning and crystalized intelligence can even improve with age (Botwinick & Storandt, 1974; McArdle, 2002; Park et al., 2002). However, the majority of older adults experience marked decline in cognition, including processing speed, memory, spatial ability, and reasoning (Salthouse, 1996) (Kramer et al., 2004). Longitudinal epidemiological studies suggest that the cognitive aging process is part of a lifespan development, and that midlife behavioral and lifestyle factors have considerable impact: a healthy diet (Kesse-Guyot et al., 2012), maintaining cardiovascular health (D. Knopman et al., 2001; Swan et al., 1998), obesity (Fitzpatrick et al., 2009), physical and social activities (Friedland et al., 2001), as well as moderate alcohol and no tobacco use (Anttila et al., 2004) seem to be protective of cognitive functioning. However, 'protective' does not mean that individuals that comply with these lifestyles will never transition to pathological aging. Though drawing that line between 'normal' versus 'pathological aging' is close to impossible. However, there seem to be a few aspects that highlight changes, indicating early alterations, like the observation of decreased speed or executive tasks in healthy older adults with microbleeds (Meier et al., 2014), signifying that those domains may be the most sensitive to vascular pathology or subtle age-associated brain changes (Nyenhuis et al., 2004). Such decline could denote future cognitive decline related to AD, even more so when taking into consideration that in healthy adults over 60, fibrillar Aβ was associated with reductions in processing speed, working memory and reasoning, but not declarative memory, a hallmark of frank AD pathology (Rodrigue et al., 2012). However, these observations do not answer the question whether vascular and fibrillar forms of amyloid reflect the same pathology and contribute independently to cognitive outcomes. But the fact that both can be present in non-demented older adults and are related to variability and decline in cognition suggests

that the distinction between normal and pathological cognitive aging may be a gradual, transitional rather than a categorical distinction. This view is supported by the epigeneticists Maloney & Lahiri (Lahiri et al., 2016), who argue that "epigenetic evidence suggests that dementia is not a suddenly occurring and sharply delineated state, but rather a gradual change in crucial cellular pathways, that transforms an otherwise healthy state, as a result of neurodegeneration, to a dysfunctional state", and add that insights from epigenetics could lead to discover preventative techniques before clinical dementia and thus maintain healthy cognitive aging.

One of the defined gray areas in cognitive aging and AD research that has gained more and more attention is the concept of mild cognitive impairment (MCI), described previously as subjective memory complaint and decreased cognitive performance in at least one domain based on normative tests (Albert et al., 2011), but without functional impairment. Mild cognitive impairment is thought to be a transitional stage between normal aging and AD, and research has indeed shown that subjects with MCI have a higher chance of developing AD (Gallagher et al., 2010; Petersen, 2004). Furthermore, there is a 4-20% annual conversion rate from amnestic MCI (a variant in which the memory domain is affected) to AD in clinic-based populations (Dickerson, Sperling, Hyman, Albert, & Blacker, 2007; Landau et al., 2010), but only a 5.4% annual incidence rate from MCI to AD in a community cohort (Manly et al., 2008). Contrary to the mentioned protective lifestyle factors, an unhealthy lifestyle can have a direct impact on cognition as well: fat intake is associated with cognition and risk for MCI later on (Eskelinen et al., 2008), midlife vascular risk factors are related to reduced cognitive performance, atrophy, and dementia at older age (Kivipelto et al., 2001; D. S. Knopman, Mosley, Catellier, Sharrett, & Atherosclerosis Risk in Communities, 2005; Launer, 2005; Nishtala et al., 2014), and midlife blood perfusion is associated with Alzheimer's pathology deposition later on (see Chapter 7.4) However, studies also show that a number of subjects that were once diagnosed with MCI convert back to 'normal cognition' (Roberts et al., 2014; Manly et al., 2008) further exemplifying that we seem to be missing important information in our observations to distinguish healthy aging from AD, and making it disputable whether the current tools that we have available may not be sufficient to pick up on the underlying pathology causing the disease.

Ideally, instead of relying on pathological definitions that are not assume to be conclusively proven, it would be more meaningful to orient ourselves on the actual clinical syndrome of AD in a top down fashion: Focusing on a phenotype, that clinicians can classify reliably, particularly in a multidisciplinary setting, could account for different cognitive profiles and allow diverging aging trajectories and disease pathogenesis. Radiological- and biomarker findings could support those

observations, and together should guide our research and hypotheses, rather than a bottom up approach of *a priori* defined pathological conventions that might depict merely the end-products of a diseased brain.

5.3 Vascular contributors to Alzheimer's disease (AD)

As mentioned earlier, vascular and cerebrovascular aspects, such as serum total cholesterol, lipoprotein(a), diabetes mellitus, atrial fibrillation, hypertension, apolipoprotein E (ApoE) levels, and atherosclerosis are risk factors for AD (Wakutani et al., 2002). Vascular pathology related to AD includes most commonly cerebral amyloid angiopathy (Z. Li et al.), which leads to injuries of the neurovasculature such as cortical small or recurrent microbleeds, lobar hemorrhages, ischemic infarcts, disorder of the blood-brain barrier (Hartz et al., 2012), and capillary closure, among others (Smith et al., 2009; Thal et al., 2009). These pathological and radiological markers have been associated with and shown to contribute to the severity of symptoms: in a study including 102 nuns, 93% of subjects with one or more lacunar infarcts (type of ischemic stroke of small, lenticulostriate arteries providing blood to deep brain structures) had dementia compared with 57% of those without infarcts, supporting that risk factors for vascular disease and stroke are linked to cognitive impairment (Breteler, 2000). For those that did not meet criteria for AD, brain infarcts were only weakly associated with poor cognition and dementia (Snowdon et al., 1997). The high presence of atherosclerosis in the circle of Willis of AD brains and its strong association with lacunar and large brain infarcts supports the confluence of cerebrovascular disease in AD (Snowdon et al., 1997) and increased risk for dementia (Breteler, Bots, Ott, & Hofman, 1998), with 80% arterial occlusion as common as in 22.5% of AD patients and only 4.7% in non-demented elderly (Roher et al., 2003).

Esiri and colleagues (Esiri et al., 1999) provided evidence that cerebrovascular disease promotes dementia by showing that patients with only AD type pathology were normal or had solely marginally reduced cognitive function relative to controls, but those with both AD and concomitant cerebrovascular had marked cognitive decline relative to controls. They note that cerebrovascular disease seems to have a greater capacity to influence cognition especially at early stages of AD, which suggests that cerebrovascular disease may be as important as frank AD pathology in the early presentation of the disease (Esiri et al., 1999), particularly when distributed in frontal and parietal brain regions (Brickman, Muraskin, & Zimmerman, 2009). Studies on mid-life cerebrovascular risk factors, hypertension and hypercholesterolemia in particular, support these findings as they manifest as increased risk for late-life cognitive impairment and dementia (Launer, 2005)

Genetic studies show that cerebrovascular risk factors share genetic risk with clinical AD and possibly accelerate the process of AD (Decarli, 2004). The apolipoprotein E (ApoE) gene has been identified to be a major vascular susceptibility factor gene in sporadic late-onset AD cases (Rocchi, Orsucci, Tognoni, Ceravolo, & Siciliano, 2009), because of its central role in lipid metabolism (McGeer & McGeer, 1995). The ε4 allele is associated with increased cholesterol levels and risk of atherosclerosis and coronary artery disease (Marrzoq, Sharif, & Abed, 2011), as well as small vessel cerebrovascular disease (Brickman et al., 2014) and the development of CAA in AD (Premkumar, Cohen, Hedera, Friedland, & Kalaria, 1996). ApoE is involved in various aspects of neurodegeneration and repair, but could also be related to Aβ deposition, lipid transport, or antioxidant activity (Snowdon et al., 1997). Another interesting vascular susceptibility gene seems to be angiotensin I-converting enzyme (ACE1) normally expressed by endothelial, epithelial and neuronal cells (Turner & Hooper, 2002) and related to hypertension. However, it has been shown to cleave Aβ *in vitro* (Hemming & Selkoe, 2005) and *ex vivo* (Zou et al., 2007), and its variation in the efficiency of Aβ degradation has been associated with AD, with which it is positively associated (Miners et al., 2008). The elevation of ACE activity in AD could be due to increased Aβ levels and is interpreted as a physiological response to Aβ accumulation, making it a strong candidate susceptibility gene for AD (Miners et al., 2009).

Data from experimental models show that chronic vascular hypoperfusion induces oxidative stress and brain energy failure, leading to neuronal death, manifesting as cognitive impairment and the development of brain pathology as in AD (Amieva et al., 2005; Bell & Zlokovic, 2009; J. de la Torre, 2002). Experimental models show that large vessel infarcts or small striatal infarcts are larger in the presence of amyloid (Cechetto, Hachinski, & Whitehead, 2008), and that patients with small cerebral infarcts and moderate AD pathology will develop dementia. Furthermore, experiments showed that small striatal infarcts in the presence of high levels of amyloid accompany the progression in infarct size over time, with increasing degree of cognitive impairment and AD-type pathology, compared with high amyloid levels alone (Cechetto et al., 2008). These observations might also suggest that underlying systemic vascular disease processes are a primary pathological component of AD and/or that vascular disease and AD pathology contribute additively, as a second, independent hit, or synergistically, in an interactive, causative, or reflective manner, to the onset of disease.

Although the diagnosis of AD requires amyloid deposition by definition, it is known that up to 30% of older adults with amyloid show no cognitive decline (Mintun et al., 2006). In contrast, 80-100% of demented patients present with vascular pathology (atrial fibrillation, hypertension, diabetes mellitus, hypercholesterolemia, arterial stiffness, and carotid intimal-medial thickness) at death,

while only 10-30% of non-demented subjects show vascular pathological markers (Gorelick et al., 2011), bolstering the importance of vascular aspects in AD. Despite the vast body of literature pointing to a link between vascular disease and AD, some studies were unable to show a direct correlation between cerebrovascular disease and increased amyloid pathology (Jellinger, 2002; Park et al., 2014). Others suggest additive or synergistic effects in their common appearance in pathological, pathophysiological and neuroimaging aspects (Breteler, 2000; Gorelick et al., 2011; Liu et al., 2015; Snowdon et al., 1997). It appears that the neuropathology of cognitive impairment in older adults is often a mixture of AD and vascular brain damage (Gorelick et al., 2011). It is crucial to account for mechanical links between vascular disease and AD, as vascular dysregulations become more pronounced with progression of the disease due to several processes (Mentis et al., 1998) and may help shed light on the disease pathogenesis. For one, damage to blood vessel leads to endothelial dysfunction, among others, increasing blood brain barrier permeability (Iadecola, 2013), reducing its neuroprotective properties and the neuronal 'milieu' required for proper functioning of neuronal circuits (Zlokovic, 2011). Furthermore, neuronal death reduces cerebral blood flow demand and therewith the hemodynamic response of the brain (Iadecola, 2004), and amyloid in arterioles hinders the relaxation of smooth muscle cells accounting for vasodilation (Christie, Yamada, Moskowitz, & Hyman, 2001). Atherosclerosis in the cerebrovascular system additionally impairs the increase of cerebral blood flow (Iadecola, 2004). While reduction of cerebral blood flow alone may not be sufficient to cause vascular injury and ischemic cell death (Hossmann, 1994) it may alter protein synthesis necessary for normal cognition, and hence be an important factor underlying dementia, aside from reducing the brain's supply of oxygen, nutrients, and energy substrates (Zlokovic & Cox, 2001).

On a more hypothetical level, vascular factors have been postulated to contribute to the formation of senile plaques themselves, initiated by cerebral capillary bleeding (Stone, 2008). It is argued that the expression of Aβ is upregulated by ischemia, and that hemoglobin released into the neuropil binds to the Aβ and promotes its oligomerization and in this way, merging risk factors for AD and vascular disease (Stone, 2008). According to the hypothesis, Aβ oligomers form into insoluble Aβ plaques, and tissue damage may results from ischemia as well as from the toxic Aβ. There is no further evidence to support this theory, but mechanisms can be related to AD-like dementia.

In summary, we outlined evidence for vascular risk factors and vascular disease increasing the risk of dementia, including AD – a multifactorial disorder that we consider a mixture of cerebrovascular and AD pathology – which often affect frontal and parietal brain regions, indicating a particular regional vulnerability of the underlying vascular system. In the next section, we will look at two vascular risk markers more specifically for a better understanding of the subsequently presented

studies: first, we will describe the role of cerebral microbleeds as a reflection of cerebral amyloid angiopathy in association with the aging brain, and will then elucidate the role of white matter hyperintensities (WMH).

5.3.1 Microbleeds as a marker of cerebral amyloid angiopathy

Microbleeds are small punctate lesions best visualized on T2*-weighted gradient-recalled echo (GRE) MRI, manifesting as a hypointense signal due to hemosiderin deposition. They are small foci of chronic blood products in brain tissue, indicative of mostly soluble Aβ40 rather than Aβ42 on the outer aspects of the artery wall (Weller, Preston, Subash, & Carare, 2009). Criteria for the identification of microbleeds include black, round or ovoid lesions (rather than linear), blooming effect on T2*-weighted MRI, at least half of the lesion surrounded by brain parenchyma (Figure 1), and distinct from other potential mimics such as partial volume artifacts, iron or calcium deposits, bone, or cavernous malformations.

The GRE pulse sequence is most apt for the detection of microbleeds (Greenberg et al., 2009). Several MRI parameters such as pulse sequence, spatial resolution, slice thickness, magnetic field strength, and image post-processing affect microbleed detection (Greenberg et al., 2009), hence estimation of presence of microbleeds may vary greatly, depending on the imaging protocol used. There are currently no widely implemented automated processes for the detection of microbleeds. The sensitivity of detection of microbleeds increases with higher field-strength MR. Studies have shown, for example, that 7T MRI was able to detect twice as many microbleeds than conventional lower field-strength imaging (Brundel et al., 2012).

Microbleeds may occur in lobar or deep regions, likely related to their pathophysiology (Cordonnier & van der Flier, 2011). While deep microbleeds are thought to be due to hypertension (Vernooij et al., 2008), lobar microbleeds are considered a marker of cerebral amyloid angiopathy (Z. Li et al.), showing a posterior cortical predominance (Rosand et al., 2005). Cordonnier and colleagues (Cordonnier & van der Flier, 2011) discuss lobar microbleeds as a possible link between the amyloid cascade hypothesis (Hardy & Selkoe, 2002), suggesting AD is initiated by abnormal cleavage of the amyloid precursor protein, leading to an imbalance of production and clearance of Aβ, and the vascular hypothesis showing the importance of vascular pathology in the pathogenesis of AD (Breteler, 2000;de la Torre, 2004; Snowdon et al., 1997). It is hence possible that brain microbleeds, simultaneously expressing vascular damage and amyloid deposition, provide a bridge between the two ideas.

Risk factors associated with microbleeds include, as stated above, ApoE genotype (O'Donnell, Rosand et al., 2000; Vernooij et al., 2008), stroke (Cordonnier, Al-Shahi Salman, & Wardlaw, 2007; Koennecke, 2006; Viswanathan & Chabriat, 2006; Vernooij, 2008), lobar hemorrhages, capillary occlusion, blood-brain-barrier dysfunction (Hartz 2012; Smith 2009; Thal 2009). They are commonly associated with cognition cross-sectionally (Poels et al., 2012; Hilal et al., 2014) as well as longitudinally (Chiang et al., 2015), and in particular with executive dysfunction (Patel et al., 2013; Qiu et al., 2010; Werring et al., 2004). The association between microbleeds and cognition will be discussed in more detail in Chapter 8 (empirical part).

In the overall population, microbleeds are found in 27% of our own community-study subjects (age average: 80 years) (Wiegman et al., 2014), and up to 38% of individuals over age 80 (Vernooij et al., 2008), but appear more frequently (78%) in AD patients (Brundel et al., 2012; Vinters & Gilbert, 1983). A predominance of lobar (vs. deep) microbleeds is found in AD patients with microbleeds, primarily located in posterior regions (92%) (Pettersen et al., 2008). Simultaneously, microbleeds are associated with elevated CSF p-tau levels (Chiang et al., 2015), and with more white matter hyperintensities (WMH), co-localized in parieto-occipital regions and reflecting small vessel cerebrovascular disease commonly seen in elderly and AD patients (Smith et al., 2010).

Moreover, patients meeting criteria for CAA test positive for Aβ binding with Pittsburgh Compound B (PiB) (Johnson et al., 2007), a radiotracer highlighting Aβ deposits, suggesting that PiB PET is unable to disambiguate vascular from fibrillar amyloid (Dierksen et al., 2010) and therefore ask to show restraint in interpretation and attribution of effects. However, a reduction in soluble Aβ prevents progression of CAA in transgenic mouse models (Gregory et al., 2012).

Another context in which cerebral microbleeds appear is in clinical trials, where they are considered a marker of immunotherapy-related adverse events (Amyloid-Related Imaging Abnormalities, ARIA) (Sperling, Jack et al., 2011). Their phenotype can be either due to microHemorrhage and hemosiderosis (ARIA-H) or vasogenic edema and sulcal effusions (Aria-E), related to altered Aβ trafficking in those individuals, and were first observed in phase I and II clinical trials of a humanized monoclonal antibody (bapineuzumab) (Yates, Villemagne et al., 2013). ARIA-E appeared with increased risk in patients treated with higher doses of amyloid therapy and ApoE4 homozygotes, but showed no gender- or age-specificity nor association with WMH or presence of microbleeds at baseline. Although ARIA-E did precede or coincide with ARIA-H, they are not spatially related and suggest disruption of vascular integrity rather than local damage (Yates et al.,

2013). Spontaneous ARIA-E, in contrast, is uncommon, but has been reported with other Aβ immunotherapeutic agents (Ostrowitzki et al., 2012). It is currently debated that microbleeds may be due to focal damage or represent a more generalized process (such as CAA), and may not directly cause neural injury, but lead to local inflammatory response and leakage of blood plasma into the brain parenchyma, leading to neuronal dysfunction and cell death (Rosidi et al., 2011), which could make them an interesting target for trials themselves.

5.3.2 Small vessel disease: White Matter Hyperintensities (WMH)

White matter hyperintensities are areas of increased bright signal best visible on T2-weighted MRI FLAIR sequences, distributed throughout the brain in either deep tissue and subcortical gray matter nuclei, or contiguous with the walls of the lateral ventricles (Malloy, Correia, Stebbins, & Laidlaw, 2007). Increased WMH volume has been consistently associated with aging, traditional vascular risk factors (Brickman et al., 2008; Dufouil et al., 2001), arterial hypertension (Pantoni & Garcia, 1997), brain metabolism and atrophy (DeCarli et al., 1995; Prins & Scheltens, 2015) and decreasing cognition (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Lee & Markus, 2006), especially in the domains of executive functioning and processing speed (Gunning-Dixon & Raz, 2000; Kloppenborg, Nederkoorn, Geerlings, & van den Berg, 2014), as well as memory (Meier et al., 2012; Smith et al., 2011). They are through to reflect small vessel cerebrovascular disease due to perfusion abnormalities and may affect cognitive functioning through disruption of intra-cerebral connectivity, having a deleterious effect on neuronal transmission (Brickman et al., 2009). Research suggests that WMH burden increases with age, among non-demented elderly (Coffey et al., 1992; DeCarli, Fletcher, Ramey, Harvey, & Jagust, 2005; Pfefferbaum et al., 1994) as well as individuals with MCI and even more severely with AD (Gootjes et al., 2004).

WMH are more commonly distributed in frontal and parietal lobes (Gootjes et al., 2004; Tullberg et al., 2004; Wahlund et al., 2001; Yoshita et al., 2006). Current research suggests an anatomical dissociation of WMH in anterior regions being increased in case of any cognitive impairment, whereas increased WMH in parietal lobes are specifically associated with amnestic MCI and AD (Brickman et al., 2009). Older non-demented adults with increased WMH burden are at higher risk for future development of AD (Vermeer et al., 2003), and WMH reliably predict conversion from cognitive normality to MCI (Smith et al., 2008) and from amnestic MCI to AD (Prasad, Wiryasaputra, Ng, & Kandiah, 2011). While WMH have been associated with memory decline

(Meier et al., 2012; Smith et al., 2011), hinting at a relationship between small vessel disease and AD, effects on episodic memory seem to be mediated by executive functioning (Parks et al., 2011).

The specific distribution and progression of WMH in parietal lobes predict incident AD (Brickman et al., 2015), and correlates with the propensity of amyloid angiopathy occurrence (Vinters & Gilbert, 1983) and reduced metabolism (Ishii et al., 2006; Jagust et al., 2002), drawing the attention to the underlying vascularization.

More recent research has shown that the WHM are increased in Aβ+ subjects compared to Aβ- subjects (Kalheim, Bjornerud, Fladby, Vegge, & Selnes, 2016). Furthermore, WMH are associated with internal carotid artery blood flow velocity and blood pressure (Aribisala et al., 2014), and increased in APOE E4 carriers in parietal lobes (Brickman et al., 2014), hence they seem to embody another important vascular aspect and may represent a common mechanistic link between vascular factors and AD, helping to shed light on the pathogenesis and expression of Alzheimer's disease.

Based on the described caveats in the definition of AD as well as the clinical relevance of vascular factors in onset and progression of AD, we tested the effects of lobar microbleeds, our main risk marker for this work, as independent variable in the context of various research studies and hypotheses, which will be outlined in the first three studies. While the first study is examining longitudinal cognitive changes in the presence of microbleeds, the second will test whether high-resolution 7T MRI is a useful tool for microbleeds detection associated with cognition in healthy, relatively young adults. The third study will examine the common appearance of lobar microbleeds and WMH. An experiment on vascular amyloidosis and quantitative perfusion loss drew our attention to a related, topic: Maier and colleagues (Maier et al., 2014) found that microbleeds may cause decline in regional cerebral blood flow (rCBF) in a transgenic mouse model of AD. As longitudinal studies that examine 'normative states' years before disease onset and in the absence of pathology are revealing for any disease process, we decided in a fourth study to examine normative blood flow in young adults before any pathology, and compare their regional perfusion patterns with amyloid deposition in a group of older adults. Taken together, we want to show how early vascular and metabolic factors impact disease pathogenesis and emphasize their predictive value prior to disease onset.

6 Aims and research questions

The primary goal of this work was the examination of cerebrovascular risk markers appreciated through neuroimaging in the context of aging and Alzheimer's disease.

6.1 Study 1 – Aims and research questions

The aim of this study was to examine the relationship between lobar cerebral microbleeds and executive functioning decline over time. The aim was addressed in an ongoing community-based longitudinal study, in which subjects were evaluated every 18-24 months.

Based on earlier studies (Cordonnier & van der Flier, 2011; Greenberg et al., 2009; Pantoni, 2010; Werring et al., 2004), we expected subjects with 'probable' CAA (two or more cerebral microbleeds; BOSTON criteria (Greenberg et al., 2009) for more details, see Chapter 6a)) to perform cognitively worse than subjects without probable CAA.

To our knowledge, there have not been any previous longitudinal studies that tested the relationship between cerebral lobar microbleeds and cognitive decline in healthy older adults. However, based on the clinical study of Gregoire and colleagues, who found an association of cerebral microbleeds with executive impairment after a 5.7-year follow-up in a stroke sample, we hypothesized subjects with two or more microbleeds to show a steeper decline in cognition than subjects with less than two microbleeds (Gregoire et al., 2012).

6.2 Study 2 – Aims and research questions

The aim of this study was to test whether high resolution MRI scanning and hence increased sensitivity is a useful tool for microbleeds detection, and whether there are neuropsychological correlates of microbleeds in healthy, relatively young older adults. This goal was achieved by examining the relationship between presence of microbleeds derived from 7T MRI and cognition in 15 adults without dementia (mean age: 68 (SD=5.15)).

Previous studies showed that the use of 7T results in the detection of twice the amount of cerebral microbleeds than lower field strength (Brundel et al., 2012), which made us confident that even at a relatively young age, we would be able to detect microbleeds and an association with cognitive performance.

Brundel and colleagues (Brundel, Kappelle, & Biessels, 2014) examined the relationship of cerebral microbleeds at 7T MRI with cognition in patients with and without type 2 diabetes and other small vessel disease, and did not find any differences between the two groups. However, our aim was to test the association of microbleeds and cognition in healthy subjects, and based on our previous findings (Study 1), we hypothesized that subjects with lobar microbleeds perform worse on tests of executive functioning than subjects without lobar microbleeds.

6.3 Study 3 – Aims and research questions

The aim of this study was to examine the relationship between regional WMH burden cross-sectionally and longitudinally and cerebral amyloid angiopathy. This goal was achieved by analyzing MRI scans of subjects from an ongoing longitudinal community-based study on aging and dementia.

Cerebral amyloid angiopathy as well as WMH have been associated with increased age (Pfefferbaum et al., 1994) as well as cognitive decline and dementia (Brickman et al., 2008; Raz & Rodrigue, 2006). A more posterior distribution of WMH was associated with strictly lobar microbleeds (Thanprasertsuk et al., 2014).

Since the regional burden of WMH seems to be non-uniform (Brickman, Muraskin, & Zimmerman, 2009), and microbleeds have a predisposition to occur in frontal and parietal brain regions, we hypothesized that subjects with microbleeds show a higher amount of WMH volume in those brain areas, as well as a higher increase of WMH volume over time, suggesting that the two markers of small vessel cerebrovascular disease may in fact reflect the same underlying pathology.

6.4 Study 4 – Aims and research questions

While most studies on blood flow related to Alzheimer's disease focus on blood flow reduction in the presence of amyloid, little is known about *normal* brain activity and metabolism years before any age-related pathology. The aim of this study was to examine independent, normative blood flow in regions that are later associated with amyloid deposition. The results were achieved by using a normative SPECT atlas from healthy, young adults, correlated with PET-derived amyloid uptake values in older adults.

Cross-sectionally, amyloid deposition is associated with diminished regional cerebral blood flow pattern in older adults (Cselenyi & Farde, 2015), and amyloid itself causes hypoperfusion in corresponding brain regions (Princz-Kranz, Mueggler, Knobloch, Nitsch, & Rudin, 2010). However, highly interconnected brain regions with high rates of ATP generation, suggesting increased neural activity (Jagust & Mormino, 2011), have more amyloid. Similarly, areas of increased metabolism in normal young adults are spatially correlated with amyloid deposition, indicating that high metabolic demand may promote amyloid deposition (Vlassenko et al., 2010). Hence, we hypothesized that regions of increased normative blood flow in young adults are associated with higher amyloid deposition later on.

7 Methods

7.1 Participants

The following studies were performed on several samples of older individuals, and consisted of cross-sectional as well as longitudinal observations. All samples either stem from the Memory Clinic at the Division of Psychiatry Research and Psychogeriatric Medicine, University of Zurich, or from an ongoing community-based aging study from the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University, New York. The primary aim was to test the role of hypothesized vascular markers in cognitive aging and AD, with special attention to lobar microbleeds that potentially contribute to the rate and severity of cognitive decline and AD.

University of Zurich

Participants from Zurich were recruited from the outpatient population of the Memory Clinic or through advertisement in local media, as well as inquiries of caregivers or relatives of patients in the case of healthy controls. A multidisciplinary team made diagnoses at consensus under the supervision of an experienced psychiatrist and in accordance with Winblad criteria for MCI (Winblad et al., 2004) and McKhann (McKhann et al., 2011) criteria for AD. Further details about inclusion criteria will be discussed in the empirical parts (Chapter 8).

Visits included a series of additional tests, such as the cognitive disorder Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), Hamilton Rating Scale for Depression (Hamilton, 1960) or Hospital Anxiety and Depression Scale – Deutsche Version (HADS-D) (Herrmann-Lingen, 2011), screening for cognitive functioning Clinical Dementia Rating scale (CDR) (Morris, 1993), comorbidity Cumulative Illness Rating Scale (CIRS) (Salvi et al., 2008), and Instrumental Activities of Daily Living (IADL) (Lawton & Brody, 1969) as well as examination of psychiatric, neurological and internal diseases or other disorders potentially causing cognitive impairment.

MRI scans were performed at baseline and follow up visits. PiB PET scans were performed at the PET Center of the Division of Nuclear Medicine, Zurich University Hospital (GE Discovery PET/CT scanners) at baseline only at the time of data analysis (for details, see Steininger et al., 2014).

All studies were approved by the cantonal ethics committee of Zurich, Switzerland and only included subjects that had given written informed consent. More details on subsamples will be provided in the corresponding empirical sections.

Columbia University, New York

Participants from the studies carried out at Columbia University in New York came from an ongoing aging study in Northern Manhattan, beginning in 1992 and 1999 respectively. Recruitment procedures and sampling strategies have been described in detail in Tang (Tang et al., 2001). Briefly, participants were all English- or Spanish speaking and tested in their language of preference. They were evaluated at 18-24 months intervals and received full medical, neurological, and neuropsychological examination at baseline and follow-up. Furthermore, race and ethnicity (vis-à-vis the 1990 US Consensus guidelines) as well as history of vascular risk factors was assessed by self-report (Luchsinger et al., 2005). Study-specific details will be provided in the according empirical sections (Chapter 8).

7.2 Neuropsychology

University of Zurich

The neuropsychological test battery from University of Zurich comprised the CERAD-plus test battery (Thalmann, 1997), Verbaler Lern- und Merkfähigkeitstest (VLMT) (Helmstaedter, 2001), nonverbal and verbal Paired Association tests (Wechsler Memory Scale-Revised (WMS-R)) (Härting, 2000), and recall of the Rey-Osterrieth Complex Figure (ROCF) (Meyers, 1995) for verbal and nonverbal memory functions. Executive functions were tested with Trail Making Test (TMT) ratio B/A (Reitan, 1958), Stroop interference score (Troyer, Leach, & Strauss, 2006), ROCF copy (Meyers, 1995), category and letter fluency (Aschenbrenner, 2000), Five-Point Test (Regard, Strauss, & Knapp, 1982), and Visual and Verbal Memory Span backward (WMS-R) (Härting 2000). TMT A and B (Reitan 1958) as well as Visual and Verbal Memory Span forward (WMS-R) (Härting, 2000) were administered to test attention and psychomotor speed. Boston Naming Test (BNT) (Thalmann, 1997) was used for testing language abilities, Clock Drawing Test (Rouleau, Salmon,

Butters, Kennedy, & McGuire, 1992) and copy of the ROCF for visuo-constructive and visuo-spatial abilities (Meyers, 1995).

Columbia University, New York

Cognition was assessed with a comprehensive neuropsychological battery. For the domains memory, language, speed/executive functioning, and visuospatial abilities, summary scores were derived. They were calculated through exploratory and confirmatory factor analyses and represented on a z-distribution (Siedlecki et al., 2010). The included tests comprised the Selective Reminding Test (SRT) (Buschke & Fuld, 1974), the modified 15-item Boston Naming Test (Kaplan E, 1983), and two tests of verbal fluency: the Letter Fluency test and the Category Fluency test. Furthermore, the Benton Visual Retention Test (BVRT) (Benton, 1955), the Rosen Drawing Test (Rosen, 1981), the Similarities test as a subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981), the Identities and Oddities test from the Mattis Dementia Rating Scale (Mattis, 1976), the Repetition task as a subtest of the Boston Diagnostic Aphasia Evaluation (BDAE) (Goodglass, 1983), the Comprehension test of the BDAE, and, in a subset of the sample, the Color trials 1 and 2 to assess processing speed (Siedlecki et al., 2010).

7.3 Imaging: MRI/PET/SPECT

University of Zurich

The two studies at University of Zurich follow two different scan protocols. For the first one, subjects were scanned on a high-resolution 7Tesla Philips Achieva (Philips Healthcare, Cleveland, OH, USA) whole-body MRI scanner at the Institute for Biomedical Engineering at University of Zurich and ETH Zurich to obtain gradient echo images (GRE) for microbleeds detection. The scanner was equipped with a nova medical quadrature transmit head coil and 32-channel receive coil array (Nova Medical, Wilmington, MA, USA). (For more details, see Steininger et al., 2014).

For the other study, PET scans were performed at the PET Center of the Division of Nuclear Medicine, Zurich University Hospital (GE Discovery PET/CT scanners) for mean PiB uptake measures. More information on PiB synthesis and PET acquisition can be found elsewhere (Gietl et al., 2015; Riese et al., 2015).

Furthermore, we used a single-photon emission computed tomography (SPECT) atlas for this study to gain insight into normative regional blood flow. Data stem from the Society of Nuclear Medicine Brain Imaging Council and are publicly available (www.brainscans.indd.org/brncnc14.htm). Details on subject recruitment and image acquisition are described elsewhere (Holland et al., 2008).

Columbia University, New York

For the studies at Columbia University, gradient echo (GRE) scans for microbleed detection as well as fluid attenuated inversed recovery (FLAIR) scans for the quantification of WMH were acquired at the Neurological Institute at Columbia University on a 1.5 Tesla Philips Intera MRI scanner (Best, the Netherlands). (For more details, see (Steininger et al., 2014)).

The choice of several samples from different locations and the collaborative dissertation was based on optimal criteria to answer the posed research questions. While University of Zurich provided excellent data on a high resolution 7T MRI scanner for microbleeds reliability and novelty in its association with cognitive aging, as well as PiB PET data in a selected sample of healthy older adults, Columbia University offered an ample dataset for image analysis from a large ongoing aging study in an ethnically diverse community cohort, and was the source of developer software relevant for specific data processing procedures and analyses.

Boston criteria for microbleed detection

For all microbleed ratings, we applied Boston criteria for diagnosis of CAA-related hemorrhage, defined as the following (Knudsen, Rosand et al., 2001):

- Definite CAA: full postmortem examination demonstrating:
  a) Lobar, cortical, or corticosubcortical hemorrhage
  b) Severe CAA with vasculopathy
  c) Absence of other diagnostic lesion
- Probable CAA with supporting pathology: clinical data and pathological tissue (evacuated hematoma or cortical biopsy) demonstrating:
  a) Lobar, cortical or subcortical hemorrhage
  b) Some degree of CAA in specimen
  c) Absence of other diagnostic lesion
- Probable CAA: clinical data and MRI or CT demonstrating:
  a) Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
  b) Age ≥55 years
  c) Absence of other cause of hemorrhage
- Possible CAA: clinical data and MRI or CT demonstrating:
  a) Single lobar, cortical, or sorticosubcortical hemorrhage
  b) Age ≥55 years
  c) Absence of other cause of hemorrhage

8 Empirical data

8.1 Study 1: Lobar microbleeds are associated with decline in executive functioning in older adults

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Published in:

Cerebrovascular Diseases, 2014; 38(5):377-83

Keywords: microbleeds, cognition, cerebral amyloid angiopathy, MRI, longitudinal

Acknowledgment: This work was supported by grants from NIH (AG034189, AG037212, AG042483), the VELUX Foundation, and the Synapsis Foundation.

Abstract

Background: Normal aging is associated with decline in cognitive abilities, particularly in the domains of psychomotor speed and executive functioning. However, "aging," per se, is not a cause of cognitive decline but rather a variable that likely captures multiple accumulating biological changes over time that collectively affect mental abilities. Recent work has focused on the role of cerebrovascular disease as one of the biological changes. In the current study, we examined whether lobar microbleeds, magnetic resonance imaging (MRI) signal voids due to hemosiderin deposits secondary to cerebral amyloid angiopathy, are associated with cognitive decline in normal aging. Previous studies that reported a relationship between the presence of lobar microbleeds and decreased cognitive abilities have been primarily cross-sectional. Here, we used a retrospective longitudinal design to examine whether the presence of lobar microbleeds is associated with the rate of cognitive decline among non-demented older adults.

Methods: Participants came from an ongoing longitudinal community-based aging study, in which subjects are evaluated at 18-24 month intervals and received a full medical, neurological, and neuropsychological examination at each of the follow-up visits. Gradient echo MRI scans were available on 197 non-demented participants (mean age: 84.15+/-5.02 years). Microbleeds were rated visually on horizontal view and divided into subcortical (basal ganglia, cerebellum) and lobar (frontal, temporal, parietal, occipital lobe) regions, and confirmed with coronal and sagittal view to exclude artifacts. Cognition was assessed with a neuropsychological battery, providing summary scores for memory, language, executive, and visuospatial abilities calculated through exploratory and confirmatory factor analyses. Using general estimating equations (GEE), we compared cognition cross-sectionally between individuals with 2 or more (n=11) and fewer than 2 (n=186) lobar microbleeds and examined longitudinal cognitive change beginning 9.47 (+/-3.13) years before the MRI scan.

Results: Subjects with 2 or more lobar microbleeds had worse executive functioning at the visit closest to the MRI scan (β = -0.044; $p<0.001$) and had faster decline in executive function over time (β=-.072, p=.012) than subjects with fewer than 2 lobar microbleeds. The two groups were similar in age at scan date, education, ethnicity, sex distribution, and cognitive performance at first visit.

Conclusions: Lobar microbleeds are associated with an accelerated rate of executive function decline. The presence of cerebral amyloid angiopathy may be an important source of cognitive decline in aging. Future work should examine how cerebral amyloid angiopathy interacts with neurodegenerative processes, such as Alzheimer's disease.

Introduction

Over the past several decades, there have been myriad efforts to characterize the nature of age-associated cognitive decline. Most studies agree that aging is associated with a gradual loss of cognitive abilities, with increasing variability or individual differences (Hultsch, 2004; Raz et al., 2005; K. W. W. Schaie, S.L., 2011) particularly in the domains of psychomotor speed and executive function (Grieve, Williams, Paul, Clark, & Gordon, 2007). "Aging," per se, is not a cause of cognitive decline but rather a variable that likely captures multiple accumulating biological changes over time that collectively affect mental abilities.

There are currently no accepted definitions of what constitutes "normal" *versus* "pathological" cognitive aging. Typically, we consider normal cognitive aging as decline in certain cognitive abilities in the absence of frank disease or evidence of neurodegenerative pathology (Daffner, 2010). Several authors have argued that small vessel cerebrovascular disease is a primary source of normal cognitive aging (Gunning-Dixon & Raz, 2000; Pantoni, 2010; Ylikoski et al., 1993). "Pathological cognitive aging," on the other hand typically refers to cognitive decline that is due to a neurodegenerative condition (Yanker, 2008). In the case of Alzheimer's disease (AD), the most common cause of pathological aging, current hypothetical pathogenic models emphasize the precipitating role of fibrillar forms of beta amyloid protein and tau pathology, which ultimately cause neurodegeneration and the neuropsychological syndrome associated with the disease (C. R. Jack, Jr. et al., 2010). The amyloid cascade hypothesis suggests that imbalance of production and clearance of Ab is a primary driver of pathological cognitive aging.

Recent literature, however, implicates small vessel cerebrovascular disease as an important source of dysfunction in AD and perhaps disease pathogenesis (Pantoni, 2010), suggesting some overlap between factors that promote cognitive decline due to normal aging and due to AD. Cerebral amyloid angiopathy (Z. Li et al.), or the deposition of beta amyloid in blood vessel walls, may represent a mechanistic link between amyloid-centered hypothesis and the increasing attention towards vascular factors in AD pathogenesis - - promoting cognitive decline in individuals without dementia but also contributing to the pathogenesis of AD. Cerebral amyloid angiopathy manifests radiologically as cerebral microbleeds (MB) distributed in lobar regions on gradient echo (GRE) and susceptibility weighted (SWI) magnetic resonance imaging (MRI) (Cordonnier & van der Flier, 2011; Greenberg et al., 2009). Thus, lobar microbleeds are considered a radiological indicator of the presence of underlying CAA and associations with clinical characteristics involving microbleeds can be attributed to the role of the underlying amyloid pathology. Previous studies showed that lobar microbleeds are associated with reduced cognition cross-sectionally (Goos et al., 2009; Poels et al., 2012; Werring et al., 2004), and that individuals with AD have a greater number of microbleeds (Pettersen et al., 2008) and CAA (Nakata-Kudo et al., 2006) compared with healthy individuals.

However, efforts to examine longitudinal cognitive change as a function of microbleed status are scarce and have only been carried out in clinical populations (Gregoire et al., 2012). There are no studies to our knowledge that have examined the association of CAA, appreciated radiologically as microbleeds, and longitudinal cognitive change among non-demented older adults. In the current study, we used a retrospective longitudinal design to examine whether community-dwelling individuals with 2 or more lobar microbleeds, as an indicator of CAA, had a more precipitous rate of cognitive change than individuals with fewer than 2 microbleeds.

Materials and Methods

Participants

Subjects came from an ongoing longitudinal community-based study of aging and dementia in northern Manhattan, which had two recruitment waves beginning in 1992 and 1999. Participants were all English or Spanish speaking, over age 65, and either White, Hispanic, or African American. Recruitment procedures and sampling strategies have been described in detail previously (Tang et al., 2001). Participants were evaluated at 18-24 month intervals and received a full medical, neurological, and neuropsychological examination at each of the follow-up visits. Beginning in 2005, participants not meeting criteria for dementia at their previous follow-up visit were invited to participate in an MRI study (Brickman et al., 2008). Seven hundred sixty-nine participants underwent high resolution initial MRI.

Beginning in 2009, participants with initial MRI scans were invited for a follow-up MRI scan, leading to a total of 339 subjects with repeat MRI; 243 of the 339 had T2*-weighted gradient echo (GRE) scans for microbleed assessment (A. F. Wiegman, Meier, I.B., Provenzano, F.A., Schupf, N., Manly, J.J., Stern, Y., Luchsinger, J.A., & Brickman, A.M. , in submission). For the current analysis, we examined cognition data starting in 1999 and excluded subjects meeting clinical criteria for dementia at the time of the GRE MRI scan (N=46), resulting in a sample of 197 subjects (mean age: 84.15+/- 5.02 years) that comprised the study group reported here. The average time between the baseline cognitive assessment and the subjects' GRE MRI scan was 9.47 (SD=3.13) years, with an average of 4.7 visits per subject (range: 3-11). The GRE MRI scan was conducted at the visit closest to the last neuropsychological examination included in current study.

MRI protocol

High-resolution three-dimensional T2*-weighted GRE images (TR=45ms, TE=31ms, flip angle= 13, slice thickness= 2mm, in plane resolution 1x1mm) were acquired on a Philips Intera 1.5 Tesla MRI scanner (Best, the Netherlands) for microbleed quantification. Microbleeds were rated by visual inspection following the criteria put forth by the Microbleed Study Group (Greenberg et al., 2009): dark, round lesions on GRE images within the parenchyma and at least half way surrounded by a white rim. They were rated on axial slices, and confirmed by visual inspection of corresponding sagittal and coronal planes to exclude artifacts such as calcium deposits, partial volume artifacts, cavernous malformations, bone, or vessel flow voids. Microbleeds were divided into 'lobar' (frontal, temporal, parietal, occipital lobes) or 'deep' (basal ganglia, thalamus, and cerebellum) categories. Number and location of microbleeds were recorded for each subject. All microbleeds were evaluated by a blinded single operator (IBM) after establishing excellent reliability with a "gold standard" rater (SMR; intra-class correlation for reliability analysis of 20 images = 0.94).

We divided our sample into two groups: subjects with zero or one (<2) microbleeds and subjects with two or more (2+) microbleeds, indicating evidence of CAA. By focusing on individuals with 2 or more microbleeds, we increased our confidence that the experimental group had evidence of CAA because multiple lobar lesions are a strong indicator of underlying pathology and a single lesion is not uncommon among individuals without pathological evidence of CAA (De Reuck et al., 2011).

Neuropsychological evaluation

Cognitive performance was assessed with a comprehensive neuropsychological battery, and summary scores for the domains memory, language, speed/executive functioning, and visuospatial abilities were derived. Summary scores were calculated through exploratory and confirmatory factor analyses and represented on a z-distribution (Siedlecki et al., 2010).

Statistical analyses

We compared demographic characteristics at the time of scan and the first cognitive test performance between individuals with fewer than two (<2) (n=186) and individuals with two or more (2+) lobar microbleeds (n=11). A retrospective longitudinal design was used to examine the rates of cognitive decline preceding the MRI scan, beginning 9.47 (+/- 3.13) years prior to the scan, as a function of microbleed group, using general estimating equations (GEE) (Zeger & Liang, 1986). The primary effects of interest in the GEE model include Group, Time, and the Group x

Time interaction. A main effect of Time would indicate a significant change in cognitive abilities over time. A significant Group effect would indicate that subjects with two or more lobar microbleeds differ from subjects with fewer than two microbleeds at the time of first visit (intercept). A significant Group x Time interaction would indicate that the rate of cognitive change over time differs between the two microbleeds groups. We ran separate models for summary measures of memory, language, speed/executive functioning, and visuospatial abilities. The variables age at MRI scan, years of education, ethnicity, sex, and cognitive domain scores at baseline were entered into the GEE model as covariates.

Results

Individuals in the two groups were similar in age at scan date, education, ethnicity, sex distribution, and cognitive performance at the time of the first visit (Table 1, Chapter 10.1). The prevalence of microbleeds in the entire sample was 27.2%. The 11 subjects with 2+ lobar microbleeds had a mean number of 4.45 microbleeds (+/-3.205). In the <2 microbleeds group, 30 subjects had one lobar microbleeds and 156 subjects had no microbleeds. Six subjects had both deep and lobar microbleeds. We re-ran the analyses excluding these subjects and the reported effects did not change notably.

Table 2 displays the results of the GEE analysis. For speed/executive functioning, both groups declined over time (significant main effect of Time) but participants with 2+ microbleeds declined at a faster rate than those with <2 microbleeds (significant Group X Time interaction; see Figure 1). The two groups had similar speed/executive functioning performance at their first assessment (non-significant main effect of Group). Of the covariates in the model, age, education, baseline cognition, but not sex, were associated with speed/executive functioning.

For the other cognitive domains, the rate of cognitive decline was similar between the two microbleeds groups (non-significant Group X Time effects). Like for speed/executive functioning, both groups declined in memory and language, but not visuospatial functioning over time (significant main effects of Time). The two microbleeds groups were similar in their abilities at baseline (non-significant main effects of Group). Age, education, and baseline cognitive performance were associated with memory, language, and visuospatial functioning (see Table 2). Sex was only related to visuospatial functioning.

Discussion

We used a retrospective longitudinal design to assess the relationship between lobar microbleeds, as a marker of cerebral amyloid angiopathy, and cognitive decline. Individuals with 2 or more lobar microbleeds had an accelerated rate of speed/executive function decline over the 9-year period preceding the MRI scan relative to individuals with fewer than 2 microbleeds.

Our findings of reduced cognition in the presence of microbleeds are consistent with previous reports: microbleeds have been associated with decreased overall cognitive status, as well as lower cognitive abilities in specific domains such as psychomotor speed and executive function (Goos et al., 2009; Poels et al., 2008; van Es et al., 2011; Yakushiji et al., 2008). Werring and colleagues (Werring et al., 2004) found that 60% of individuals with microbleeds had executive dysfunction compared with 30% without microbleeds. Microbleeds also predicted executive functioning impairment 6 years later in a sample of stroke patients (Gregoire et al., 2012). Our study extends these findings by examining the longitudinal cognitive course of neurologically healthy individuals with and without evidence of cerebral amyloid angiopathy. Although the retrospective design precludes the ability to determine whether the development of the microbleeds preceded the cognitive outcomes, the findings do establish a relationship between the two. It is possible, of course, that additional factors promote the more rapid cognitive decline and also lead to the development of microbleeds. Prospective analyses will help us determine whether microbleeds promote subsequent cognitive decline in this cohort.

We observed an association of microbleeds with decline in speed/executive functioning but not in other cognitive domains. Speed or executive tasks may be most sensitive to vascular pathology or subtle age-associated brain changes in general (Nyenhuis et al., 2004). Further, accelerated decline in executive functioning may be a harbinger for future decline in cognition related to AD. It is noteworthy that among cognitively normal adults above age 60, fibrillar forms of beta amyloid, as measured by positron emissions tomography, was related to reductions in measures of processing speed, working memory, and reasoning, but not declarative memory, a hallmark feature of frank AD (K.M. Rodrigue et al., 2012). In the current study, we appear to have a similar association between vascular forms of beta amyloid and reduction in speeded tasks and executive abilities in non-demented older adults. Whether vascular and fibrillar forms of beta amyloid reflect the same pathological process and contribute independently to cognitive outcomes remains an important question. The fact that both can be present in non-demented older adults and are related to variability in cognition and cognitive decline provides compelling evidence that differences between

"normal" and "pathological" cognitive aging may be more a question of degree than of categorical distinction.

Relatively few participants in the study had evidence of cerebral amyloid angiopathy by virtue of having two or more lobar microbleeds, but this observation is consistent with what has been reported in previous community-based cohorts (van Es et al., 2011). Although reliable changes in cognition were observed among those with two or more microbleeds, we may have had limited power to detect change in other domains. Furthermore, the relatively low field strength of the MRI scanner used may have led to an underestimation of the number of microbleeds and could account for the few subjects with two or more microbleeds. On the other hand, because of the low field strength, we can be confident that individuals displaying 2 or more microbleeds do in fact have some degree of CAA. Furthermore, our sample is typical of the demography that increasingly comprises the older segment of the US population: racially and ethnically diverse individuals with a range of educational background. Previous efforts that examined associations between microbleeds and cognition generally did so among clinical patients with history of stroke (e.g., (Gregoire et al., 2012)); our findings show that CAA is a source of cognitive decline even among community-dwelling older adults that were recruited with epidemiological methods.

In a similar vein, the small number of subjects with 2 or more detectable microbleeds coupled with the relatively high number of covariates included in the GEE models may raise some concern about the reliability of the findings. To address this issue, we selected 11 individuals with <2 microbleeds matched on cognition at first visit, age, education, and sex and re-analyzed the data without demographic covariates (data not shown). The observed effects in this limited sample were of the same magnitude as those observed in the presented analyses above, increasing confidence in our findings.

We were able to exploit over 9 years of longitudinal data to examine associations between rates of cognitive decline and evidence of CAA at a single time point. To our knowledge, this is the first study to examine the longitudinal course of cognition as it relates to CAA in community-dwelling older adults. Our observations have significant theoretical and clinical implications. The findings highlight that pathological changes in normal aging and AD may be less distinct than previously thought. That is, vascular forms of beta amyloid, one of the primary pathological features of AD, are prevalent among older adults and predict rate of "normal" cognitive decline. This shared pathology between individuals with and without dementia due to AD highlights that there are other factors, besides amyloid, that might potentiate the neuropsychological syndrome that leads to dementia. Nonetheless, microbleeds may be a logical clinical treatment or preventive target to

consider when designing studies or interventions to maximize cognitive aging in general. Further, clinicians should take into account the potential role of microbleeds in diagnostic and prognostic formulations.

8.2 Study 2: Lobar cerebral microbleeds identified by 7 Tesla Magnetic Resonance Imaging (MRI) are associated with decreased executive functioning in cognitively healthy older adults

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Published in:

Currently under review

Abstract

Background: T2*-gradient echo (GRE) magnetic resonance imaging (MRI) at high field strength is thought to be a sensitive tool for detecting cerebral microbleeds.

Objectives: It is unclear whether this increased sensitivity yields clinically important information, as no effect of presence of microbleeds detected at this field strength and cognition in healthy adults has been found. Establishing this relationship is the objective of the current study.

Design: We examined differences in neuropsychological tests performance between individuals with and without lobar cerebral microbleeds.

Setting/Participants: T2*-GRE MRI scans at 7 Tesla (7T) were obtained in 15 cognitively normal older adults.

Methods: We used a neuropsychological test battery to examine cognition, and counted number of microbleeds using GRE MRI scans.

Results: At least one cerebral microbleed could be detected in 5 participants (33%). Individuals with cerebral microbleeds performed significantly worse on a test of visuospatial planning and organization (Rey-Osterrieth Test Copy) than subjects without microbleeds ($p=0.029$). No significant effects on attention, memory/learning, language, and global cognition were observed.

Conclusion: T2*-GRE at high magnetic field strength provides clinically significant information.

Key words: 7T MRI, microbleeds, cognition, cerebral amyloid angiopathy

Key points:

- Cerebral lobar microbleeds, a marker of cerebral amyloid angiopathy, acquired on high resolution 7T MRI, have not been found to be associated with cognition in healthy adults previously.
- The presence of microbleeds was associated with reduced executive abilities.
- Reliability analyses showed that high resolution 7T MRI is an appropriate tool to quantify cerebral microbleeds.

Introduction

Cerebral lobar microbleeds are prevalent in 27% to 36% of community-dwelling older adults (Chowdhury et al., 2011; Conijn et al., 2011; Poels et al., 2010; A. F. Wiegman et al., 2014) and are associated with decreased cognition, particularly executive function(Meier et al., 2014; Patel et al., 2013; Poels et al., 2012). Magnetic resonance imaging (MRI) is valid for the assessment of cerebral lobar microbleeds in clinical populations, as microbleed-related hemosiderin deposits manifest as distinct regional signal voids in T2*-gradient echo (GRE) sequences. Sensitivity for the detection of microbleeds is highly dependent on the field strength of the magnet used and T2*-GRE at high magnetic field strength of 7 Tesla (7T) results in detection of twice the amount of cerebral microbleeds than at lower field strengths (Brundel et al., 2012), thus underlining the potential of 7T-MRI for investigation of relationships between cerebral microbleeds and cognition in healthy older adults. It is likely that previous efforts underestimated microbleed prevalence among older adults, and therefore accurate impact on cognition because they relied on relatively low field strength MRI with protocols not optimized for microbleed detection (Conijn et al., 2011; Gregoire et al., 2010; Kuijf et al., 2012).

In the current study, we acquired T2*-GRE MRI sequences at high magnetic field strength in cognitively healthy older adults. We investigated presence of microbleeds in the study sample and examined differences between individuals with and without microbleeds in global cognition, attention, learning and memory, language as well as visuospatial and executive functioning. With increased field strength and associated increased sensitivity comes a higher likelihood of false positive detection. Thus, a second goal was to determine the reliability of visual detection of microbleeds at high magnet field strength.

Materials and Methods

Study population and neuropsychological assessment

Fifteen subjects from an aging and cognition study at the University of Zürich (Steininger et al., 2014) were included in this sub-study. Participants had a mean (SD) age of 68.27 (5.15) years, and were neurologically healthy without evidence for cognitive impairment as indicated by Mini Mental State Examination (MMSE = 29.5 (0.9) (Folstein et al., 1975). Exclusion criteria were cognitive deficits indicating presence of mild cognitive impairment (MCI) or dementia (Albert et al., 2011; Petersen et al., 1999), significant medication or drug abuse with possible effects on cognition, and general MRI exclusion criteria. Cognitive performance was assessed with a comprehensive neuropsychological battery (Steininger et al., 2014), covering the domains attention, learning/memory, language, and visuospatial/executive functioning. We selected performance on

two representative tests for each domain as primary cognitive outcomes, including the Trail Making Test Part A (Tombaugh, 2004) and Digit Span Forward (Hester, Kinsella, & Ong, 2004) for attention, immediate recall of a list learning test (VLMT) (M. D. Lezak, 1984) and Rey-Osterrieth Complex Figure (Watanabe et al., 2005) delayed recall for learning and memory, Letter Fluency (M. Lezak, 1995) and the Boston Naming Test (Nicholas, 1988) for language. Executive function was assessed with the Trail Making Test Part B for speed and set switching (Salthouse, 2011; Tombaugh, 2004) and Rey-Osterrieth Complex Figure Copy for 'visuospatial executive functioning' (Watanabe et al., 2005).

MRI protocol

High-resolution three-dimensional T2*-weighted GRE images (Scan duration: 385s, repetition time (TR) = 70ms, echo time (TE) = 27ms, field of view = 220 x 154 x 198mm, 220 slices, resolution=0.65x0.65x0.70mm, flip angle=27degr) were acquired on a Philips Achieva 7 Tesla MRI scanner (Philips Healthcare, Cleveland, OH) for identification of lobar cerebral microbleeds (for examples, see Chapter 10.3). Microbleeds were evaluated by a single operator (IBM). Dark, round lesions within the parenchyma and at least half way surrounded by a white rim were counted as microbleeds when detected on axial slices and confirmed by visual inspection of sagittal and coronal planes to exclude artifacts (calcium deposits, cavernous malformations, bone, vessel flow voids, partial volume artifacts) (Greenberg et al., 2009) (Figure 1). Number and location of microbleeds were recorded for each subject. Each subject's MRI scan was evaluated at two time points for determination of intra-rater reliability. Every identified microbleed was confirmed by an independent rater with experience in microbleed rating.

Statistical analyses

We compared demographic characteristics between individuals with no microbleeds and those with any microbleeds with chi-square and t-tests. Cognitive performance between the two groups was compared with independent t-tests. Because of the small sample size, we also used permutation tests for randomization. For each outcome measure, the assignment to microbleed status was randomized 10,000 times to create null-hypothesis conditions. Each time the t-statistic was computed for the random assignment to generate the actually existing, rather than theoretically formulated, t-distribution. Empirical p-levels were approximated in a two-tailed manner as the proportion of t-values in the null-distribution whose absolute values were more extreme than the experimentally observed t-value. Intra-rater reliability for microbleed detection was assessed through intra-class correlation (ICC).

Results

The two groups were similar in age, level of education, and sex distribution (Table 1). Out of the 15 subjects, five had detectable lobar microbleeds: one subject had four, one had two, and three had one microbleed. All microbleeds were found exclusively in frontal and/or parietal lobes; none of the subjects had subcortical microbleeds. The intra-rater reliability, calculated through the intra-class correlation coefficient (ICC), for microbleeds detection was high (k =0.90).

Individuals with microbleeds performed worse on Rey-Osterrieth Complex Figure copy portion than individuals without microbleeds (t=2.449, p=0.029). The two groups did not differ in performance on tests of global cognition, attention, learning and memory, language, and on the Trailmaking Test Part B (Table 2). Permutation tests, eliminating the necessity of multiple corrections, yielded the same results as the initial t-tests, with the Rey-Osterrieth Complex Figure Copy as only significant dependent variable (p= 0.0236).

Discussion

Our data indicate that presence of lobar cerebral microbleeds in cognitively normal older adults as measured using T2*-GRE at high magnetic field strength of 7T, is associated with lower performance on a task of visuospatial executive functioning. This finding is consistent with earlier publications on cognitive effects of cerebral microbleeds (Meier et al., 2014; Patel et al., 2013; Poels et al., 2012), to our knowledge this is the first study to find a relationship between T2*-GRE at 7T for assessment of cerebral microbleeds and cognition in healthy older individuals.

Previous studies demonstrated increased signal-to-noise-ratios of the T2*-GRE contrast at high field strength and increased sensitivity for detection of lobar cerebral microbleeds (Conijn et al., 2011; Kuijf et al., 2012). Reliability of our 7T measures for identification of lobar cerebral microbleeds is supported by high intra-operator agreement as well as confirmation of the presence of microbleeds by an experienced, second rater. Hence, 7T MRI seems to be a useful tool for detection of microbleeds with high sensitivity and reproducibility. In terms of clinical implications, we showed that microbleeds are present in relatively young older adults and associated with poorer performance on the Rey-Osterrieth Complex Figure, which is a visuospatial functioning task that requires planning and organization, important components of executive functioning. Despite the small sample size, our findings suggest that microbleeds detected at high field strength are associated clinically important phenomena.

Microbleeds were identified exclusively in frontal and parietal areas of the brain, which is unsurprising, given the vulnerability of these regions to vascular damage (McManus, 2005; Poels et al., 2012). A study examining stroke patients showed that subjects with additional microbleeds performed worse cognitively than subjects without microbleeds, especially when distributed in anterior regions (Werring et al., 2004). The fact that we find an association with lower test performance in the Rey-Osterrieth complex figure test is also consistent with several earlier reports on relationships between fronto-parietal brain dysfunction and deficits in executive function (Alvarez & Emory, 2006; Goldman-Rakic, 1996; Unschuld et al., 2013). The association of microbleeds with the Rey-Osterrieth Complex Figure copy but not the Trail Making Test B –our other measure for executive functioning– could be due to the Rey-Osterrieth being a more complex test, requiring higher organizational, planning, and visuospatial skills (Diamond, DeLuca, & Kelley, 1997), while the Trail Making Test B tests the cognitive flexibility aspect of executive functioning (Salthouse, 2011).

Here, our data are consistent with previous findings about cerebral microbleeds being associated with lower executive functioning (Patel et al., 2013; Poels et al., 2012), thus suggesting that the executive functioning aspects of the ROCF may be particularly sensitive to reflect brain change associated with cerebrovascular pathology (Reed et al., 2007). However, our study may have lacked statistical power to detect group differences in other cognitive domains.

While we acknowledge that the sample size (n=15) in our study is small, the novelty of using high resolution 7T MRI in association with cerebral microbleeds is a significant strength. We were unable to compare explicitly the sensitivity and specificity of microbleed detection with 7T MRI with detection with lower field strength magnets as has been done previously (Conijn et al., 2011); however, this is the first study, to our knowledge, that finds neuropsychological correlates of microbleeds detected at 7T. Future work should consider larger sample sizes and examine other correlates of microbleeds, such as glucose metabolism derived with PET scanning.

Acknowledgments: We thank all subjects for their study participation. We thank Daniel Summermatter from Division of Psychiatry Research and Psychogeriatric Medicine, University of Zuerich, Switzerland, for help in setup and administration of neuropsychological tests. This work was funded by the Swiss National Science Foundation (Schweizerischer Nationalfonds, SNF) and supported by grants from National Institute of Health (NIH) [AG034189] (to AMB), the VELUX Foundation and the Synapsis Foundation (to IBM), and institutional support from the Division of Psychiatry Research and Psychogeriatric Medicine, University of Zürich and Institute for Biomedical Engineering University of Zürich and ETH Zürich, Switzerland. There are no conflicts of interest pertaining to this publication for any of the involved authors.

8.3 Study 3: Lobar microbleeds are associated with white matter hyperintensities

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Keywords: microbleeds, white matter hyperintensities, cerebral amyloid angiopathy, MRI, longitudinal

Acknowledgment: This work was supported by grants from NIH (AG034189, AG037212, AG042483), the VELUX Foundation, and the Synapsis Foundation.

Published in:

Currently in preparation

Abstract

Background: Recent work has focused on the identification and role of cerebrovascular markers as biological changes contributing to cognitive aging and dementia. White matter hyperintensities (WMH) are areas of increased signal on T2-weighted magnetic resonance imaging thought to reflect small vessel occlusive disease. Cerebral microbleeds are MRI signal voids due to hemosiderin deposits often secondary to cerebral amyloid angiopathy when distributed in lobar regions of the brain. Although both types of lesions have been associated with suboptimal cognitive aging and dementia, the extent to which they reflect shared or independent pathology is unclear. In the current study, we examined the co-occurrence of two such markers and their regional distribution and the extent to which cerebral microbleeds are associated with the regional progression of WMH.

Methods: Participants (n=187) came from an ongoing longitudinal community-based study of aging and dementia (mean age = 85.48 +/- 5.12). They received a full medical, neurological, and neuropsychological examination and two MRI scans (mean interval: 16 months). For baseline and follow-up WMH quantification, T2-weighted FLAIR images were acquired and volumes were derived. The gradient echo (GRE) MRI scan for microbleeds visualization was only conducted at their second visit. Microbleed scans were available on 187 subjects. We examined whether regional WMH volume differed in subjects with (n=39) and without lobar microbleeds (n=148) and whether subjects with lobar microbleeds showed a higher increase in total WMH volume over time than subjects without.

Results: Subjects with lobar microbleeds showed more WMH volume in frontal and parietal lobes than subjects without ($F(3, 519)=9.82$; $p<0.001$). Subjects with microbleeds had a higher increase in total WMH volume than those without ($F(1, 173)=9.61$; $p<0.05$).

Conclusion: Lobar microbleeds are associated with more severe WMH burden in frontal and parietal lobes and have a steeper increase in WMH burden over time. Our findings suggest that CAA and progressive white matter changes may be interdependent.

Introduction

White matter hyperintensities (WMH) are areas of increased lucency visualized on T2-weighted magnetic resonance imaging (MRI), reflecting small vessel cerebrovascular disease (Wardlaw et al., 2013). The severity of WMH is associated with increased age (Pfefferbaum et al., 1994), risk for Alzheimer's disease, risk for stroke, and with lower performance across a range of cognitive tests (Brickman and Buchsbaum, 2008; Gunning-Dixon et al., 2008; Gunning-Dixon and Raz, 2000). Previous work demonstrated that the clinical manifestations of WMH vary as a function of their regional distribution. For example, we mentioned that increased parietal lobe WMH is selectively associated with genetic and clinical risk of Alzheimer's disease (Brickman et al., 2014), whereas frontal lobe WMH is a reliable predictor of mortality (Wiegman et al., 2013).

Cerebral lobar microbleeds are small punctate lesions, visualized on T2*-weighted gradient-echo (GRE) or susceptibility weighted (SWI) MRI and visible due to hemosiderin deposition (Greenberg et al., 2009; Cordonnier et al., 2011). When occurring in lobar regions, they are considered an indicator of cerebral amyloid angiopathy, the deposition of beta amyloid in blood vessel walls, and are more commonly seen with advanced age as well as dementia (Martinez-Ramirez et al., 2014). Microbleeds are as common as up to 38% of individuals over age 80 (Vernooij et al., 2008). In our general community-dwelling study population, they were found in 27% of our subjects (Wiegman et al., in submission). Given their relation to amyloid and their vascular nature, they could constitute the link between the amyloid hypothesis (Hardy and Selkoe, 2002) that suggests AD to be initiated by abnormal cleavage of the amyloid precursor protein, leading to production and clearance imbalance of amyloid, and the vascular hypothesis (Snowdon and Roberts, 1997; Breteler 2000), showing the importance of vascular pathology in cognitive aging and the pathogenesis of AD. In other words: microbleeds could be the expression of both, vascular damage and amyloid deposition.

The regional dissociation of WMH raises the possibility that the underlying pathology is not uniform (Brickman et al., 2009). White matter hyperintensities distributed in anterior regions may reflect non-specific small vessel occlusive disease; posterior distribution may be heterogeneous and include Alzheimer's pathology, such as amyloid. To test this possibility, the current study sought to examine the relationship of severity and progression of regional WMH with the presence of lobar cerebral microbleeds, an MRI marker suggestive of the presence of cerebral amyloid angiopathy (Martinez-Ramirez, 2014). We hypothesized that there would be a selective association between WMH distributed in parietal regions with the presence of microbleeds, which would suggest that WMH in this region may reflect the presence of amyloid pathology.

Materials and Methods

Participants

There were 187 study subjects came from an ongoing community-based study of aging and dementia in northern Manhattan. They were all English or Spanish speaking, over age 65, and either White, Hispanic, or African American. Recruitment procedures and sampling strategies have been described elsewhere (Tang, Cross, Andrews 2001). Participants received a full medical, neurological, and neuropsychological examination and two MRI scans. The GRE MRI sequence was included only at their second visit.

MRI protocol

White Matter Hyperintensities

For determination of WMH, fluid attenuated inverse recovery (FLAIR) T2-weighted images (TR = 11,000 ms, TE = 144.0 ms, 2800 inversion time, FOV 25 cm, 2 nex, 256x192 matrix with 3 mm slice thickness) were acquired on a 1.5 T Philips Intera scanner at Columbia University in axial orientation (Louis et al., 2008). White matter hyperintensity volumes were derived using manual and semi-automated procedures that have been previously described in detail (Brickman et al., 2011; DeCarli et al., 1996).

Microbleeds

For microbleed detection, high-resolution three-dimensional T2*-weighted GRE images (TR=45ms, TE=31ms, flip angle= 13, slice thickness= 2mm, in plane resolution 1x1mm) were collected on 187 subjects, acquired on a Philips Intera 1.5 Tesla MRI scanner (Best, the Netherlands). Microbleeds were rated by a single operator (IBM) by visual inspection. The criteria of the Microbleed Study Group (Greenberg, Vernooij, Lancet, 2009) include: dark, round lesions on GRE images within the parenchyma and at least halfway surrounded by a white rim. They were rated on axial slices and confirmed on sagittal and coronal planes to exclude artifacts like calcium deposits, partial volume artifacts, cavernous malformations, bone, or vessel flow voids. Microbleeds were divided into 'lobar' (frontal, temporal, parietal, occipital lobes) or 'deep' (basal ganglia, thalamus, and cerebellum) categories. For each subject, number and location of microbleeds were recorded. Excellent reliability with a "gold standard" rater (SMR; intra-class correlation for reliability analysis of 20 images = 0.94) was achieved. We divided our sample into two groups: subjects with and without microbleeds. To confirm results using 'probable' instead of 'possible'

diagnosis of CAA, we reran the analysis dividing our sample into subjects with fewer than two (<2) and subjects with more than two (2+) microbleeds.

Statistical analyses

In a retrospective design, we compared demographic characteristics of subjects with and without microbleeds as well as in the groups with fewer and more than two microbleeds (quantified at second MRI visit). Multivariate general linear model was used to compare WMH volume between subjects with and without lobar microbleeds in frontal, temporal, parietal, and occipital lobes (main effect of group). Analysis was repeated for total WMH volume. Furthermore, we examined whether subjects had increased total WMH volume over time (main effect of time), and whether subjects with lobar microbleeds show a higher increase in regional WMH volume over time than subjects without microbleeds (group by time interaction). The variable age at evaluation was entered into the model as a covariate.

Results

Individuals in the two groups were similar in age of evaluation sex- and ethnic distribution (Table 1, Chapter 10.4). The prevalence of microbleeds in the entire sample was 21%; 39 subjects had lobar microbleeds, 148 subjects had no lobar microbleeds. Seven subjects had both deep and lobar microbleeds. We re-ran the analyses excluding these subjects and the results did not change notably.

Figure 1 shows the results of the GLM. Subjects with lobar microbleeds showed more WMH volume in frontal and parietal lobes than subjects without lobar microbleeds ($F(3, 519)=9.82$; $p<0.001$). No group differences were found for temporal and occipital lobes. Looking at all four lobes together, subjects with lobar microbleeds had higher total WMH volume than subjects without.

Figure 2 shows the results of the longitudinal analysis: subjects increased in total WMH volume over time (significant main effect of Time), but participants with lobar microbleeds had a higher increase in total WMH volume than those without microbleeds (significant Group x Time interaction) ($F(1, 173)=9.61$; $p<0.05$). The two groups had similar amounts of total WMH at baseline (non-significant main effect of Group). The covariate age at evaluation was not associated with any of the variables in the model. Testing the hypotheses using the more conservative CAA diagnosis did not change the reported effects notably (data not shown).

Discussion

We assessed the relationship between presence of lobar cerebral microbleeds and total as well as regional WMH burden, and examined whether presence of lobar microbleeds increases total WMH severity over time. As expected, individuals with lobar microbleeds show more severe WMH burden overall, but also regionally in frontal and parietal lobes. In addition, subjects with lobar microbleeds show a more severe increase in WMH burden over time than subjects without.

Our findings of increased WMH volume in the presence of lobar cerebral microbleeds are consistent with previous reports, suggesting that CAA may cause progressive white matter changes (Chen et al., 2006).

Traditional vascular factors have been associated with WMH, such as diabetes, heart disease, obesity, and particularly hypertension (Brickman et al., 2008; Dufouil et al., 2001), as well as blood pressure fluctuation (Brickman et al., 2010). In recent studies, WMH have been associated with risk for AD, the diagnosis of AD, as well as the rate of cognitive decline (Brickman et al., 2008; Brickman et al., 2012; Luchsinger et al., 2009; Meier et al., 2012; Provenzano et al., 2013). Their parietal predominance has been specifically associated with risk of AD (Brickman et al., 2012) and predicted progression to AD in a cohort of older, community-dwelling adults (Brickman et al., in submission). These findings suggest that the accumulation of small vessel cerebrovascular disease reflected as WMH mediate the pathogenesis of AD.

Similarly, lobar cerebral microbleeds have been associated with cognitive decline cross-sectionally as well as longitudinally, and appear with a higher frequency at higher age and with AD (Yates et al., 2013). While lobar microbleeds are thought to be a reflection of CAA, WMH could be an accumulation of more unspecific vascular factors including, but not exclusively, CAA. Their simultaneous presence suggests an interaction. However, our data does not show whether the simultaneous appearance of the two markers leads to a direct interaction between the two, or whether subjects with more lobar microbleeds and higher WMH volume generally are at higher vascular risk. While it is possible that due to inflammatory markers and toxicity, the accumulation of microbleeds causes an increase in WMH volume and vice versa, it is plausible to assume that the two markers are both a reflection of the increased overall vascular risk of an individual, mirrored in different types of small vessel cerebrovascular disease.

Strengths of the current study include its large sample size and the community-based, ethnically varied sample as well as the use of quantitative multimodal longitudinal neuroimaging. Future studies should assess the individual contribution of different types of small vessel cerebrovascular disease and include longitudinal data to monitor concurrent change over time.

8.4 Study 4: Brain areas with normatively higher relative blood perfusion are more susceptible to amyloid deposition in late life

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Published in:

Currently under review

Abstract

Recent studies suggest decreased cerebral blood perfusion in areas with localized deposition of amyloid-β (Aβ), the primary pathological marker of Alzheimer's disease, but these studies are unable to disambiguate whether lower blood perfusion promotes amyloid deposition or whether amyloid deposition affects local blood perfusion. Using normative SPECT cerebral blood perfusion maps from healthy, younger adults and PET-derived amyloid uptake values in older adults (n=128, 44% women; age range: 56-87), we found that brain areas with higher normative relative blood perfusion in younger adults correlate spatially with higher amyloid uptake values in older adults ($F(3,27)=3.19$, $p=0.036$). The findings demonstrate that brain areas with relatively higher blood perfusion are at particular risk for the development of Alzheimer's pathology.

Introduction

The deposition of cerebral β-amyloid (Aβ) throughout the cortical mantel is a hallmark of Alzheimer's disease. However, amyloid pathology is not distributed uniformly (Braak & Braak, 1997b; Klunk et al., 2004; Thal et al., 2002). Recent studies have turned to the examination of perfusion patterns in the aging brain to help explain this regional variability. Diminished regional cerebral blood flow (CBF) is associated spatially with the pattern of Aβ deposition cross-sectionally (Cselenyi & Farde, 2015; Mattsson et al., 2014; McDade et al., 2014). In animal models, mild chronic cerebral hypoperfusion creates a metabolically deregulated microenvironment that triggers entry and accumulation of peripherally applied amyloid peptides (ElAli, Theriault, Prefontaine, & Rivest, 2013). On the other hand, Aβ deposition in brain arteries itself causes hypoperfusion in corresponding brain regions and subsequent neurological deficits (Princz-Kranz et al., 2010), likely via decreases in vasodilation caused by Aβ toxicity (Price, Chi, Hellermann, & Sutton, 2001). Thus, acute perturbation in blood flow potentiates amyloid pathology, which, in turn, decreases regional blood flow.

The extent to which regional blood flow over long periods of time affects the deposition of Alzheimer's pathology is less clear. Areas with relatively diminished chronic metabolism might be more vulnerable to amyloid pathology due to decreased release of cleavage products of the amyloid precursor protein (APP) thought to be linked to cerebral vasculature (Nitsch, Farber, Growdon, & Wurtman, 1993). Associations between blood flow and Alzheimer's pathology may also result from the lower density of vasculature, which is associated with blood brain barrier leakage (Cavaglia et al., 2001), and impaired clearance of pathology (Zlokovic, 2008). Conversely, higher neural activity and metabolism has been linked to increased Aβ deposition (Jagust & Mormino, 2011). In this vein, brain areas with relatively higher blood flow may be most vulnerable to the deposition of Aβ because of increased metabolic demand throughout life, which may promote Aβ deposition via chronic oxidative stress and associated inflammatory changes (Beal, 1995; Bowling & Beal, 1995; Frederiksen, Garland, Zigler, & Piatigorsky, 1996). In humans, long-term longitudinal studies that examine patterns of cerebral blood flow in early life as they relate to Aβ deposition in late life are logistically unrealistic. To address this issue, we examined the spatial distribution of fibrillary Aβ deposition in older adults as a function of normative regional cerebral blood flow values derived from an atlas created in younger, healthy adults. We tested whether increased Aβ is disproportionately present in areas that show normatively diminished or increased blood perfusion.

Materials and Methods

Subjects

One hundred and twenty-eight participants came from an ongoing aging study in the Division of Psychiatry Research at University of Zurich (Gietl et al., 2015; Riese et al., 2015; Steininger et al., 2014). All subjects underwent detailed screening and neurological and neuropsychological evaluation. Non-demented and non-depressed individuals, defined by Mini-Mental State Examination (scores≥27), neuropsychological test results, and Hamilton Depression Rating Scale (Hamilton, 1960) (17 item, score ≤12), were included in these analyses. Subjects with mild cognitive impairment (MCI) (Winblad et al., 2004) were included (n=28). Exclusion criteria included neurologic, psychiatric, or major medical illness, medication, or history of drug abuse that might affect cognition, as previously described (Gietl et al., 2015). Participant age ranged from 56 to 87, with a mean of 69.7 years (SD=6.22); 44% (n=56) were women.

PiB PET Imaging

PET scans were performed at the PET Center of the Division of Nuclear Medicine, Zurich University Hospital (GE Discovery PET/CT scanners) (Riese et al., 2015; Steininger et al., 2014). Mean PiB uptake in all cerebellar and cortical regions-of-interest (ROIs) was calculated from 5 minute frames covering the time span of 50-70 minutes after administration of the compound, using a volume-weighted averaging procedure for derivation of global cortical and cerebellar PiB uptake averaging the same ROIs of both hemispheres. The cortical to cerebellar standardized uptake value (SUVR) was calculated (Gietl et al., 2015). Frames 1-13 were averaged for co-registration with the subject's T1-weighted MR image. A maximum probability atlas was used to define ROIs based on gray and white matter segmentation of each subject's structural MRI scan (50% GM probability), which was used to derive PiB uptake values in each ROI defined in the Hammers atlas (Hammers et al., 2003). The combined transformation matrices (PET to MR and MR to Montreal Neurological Institute (MNI) space) of each participant for spatial distribution analysis were applied to the dynamic PET images to perform all further analyses in MNI space (Evans et al., 1992).

SPECT normative atlas

Single-photon emission computed tomography (SPECT) images from historical data were obtained for the creation of a blood flow atlas (Holland et al., 2008). Images came from 47 healthy adults between age 22 and 49 years (mean $\pm$ SD = 34.3$\pm$ 7.6 years). Data were made publicly available by

the Society of Nuclear Medicine Brain Imaging Council (www.brainscans.indd.org/brncnc14.htm). Details on subject recruitment and image acquisition were described previously (Holland et al., 2008). Mean relative blood perfusion was calculated in same 31 cortical regions of the Hammers atlas that were used to derive PiB SUVR values, as above (Hammers et al., 2003) to allow for direct comparison between modalities and groups. Areas of the posterior fossa, central structures, and ventricles were excluded from the blood flow analysis. Values from the same ROIs in the left and right hemisphere were averaged.

From the SPECT data, mean relative blood perfusion values of each ROI were derived over all subjects. From the PET data, a mean PiB value was derived for each ROI.

Statistical analyses

A Pearson correlation between mean relative blood perfusion values and mean amyloid was run not across subjects, but over all regions, for direct comparison of mean relative blood perfusion and PiB SUVR values in the same ROIs. For data reduction purposes, the ROIs were then grouped into quartiles based on lowest to highest relative perfusion values. Univariate analysis of variance was used to determine whether the amyloid uptake values differed across the four quartiles defined by the relative perfusion values in the younger subjects. We tested the omnibus effect and the linear trend across the four quartiles.

Results

Areas evidencing higher relative blood perfusion in younger subjects displayed increased amyloid burden in the older subjects studied (r=0.409, p=0.022; Figure 1, Chapter 10.5). Similarly, amyloid deposition values increased overall monotonically across the four relative blood perfusion quartiles (significant omnibus effect, F(3,27)=3.19, p=0.036, and effect for linear trend, p=0.029), which indicated that areas with higher levels of amyloid deposition in older adults correlated with normatively higher relative blood perfusion, although the upper two quartiles did not differ significantly (Figure 2). As seen in Figure 2, even though the linear trend was significant across the four quartiles, values in the last two quartiles were similar to each other.

Figure 3 shows the ROIs that comprise the quartile groups. Areas with the highest amyloid uptake values and blood perfusion included cuneus, lingual gyrus, insula, posterior cingulate gyrus, and pre-subgenual anterior cingulate. Areas that had relatively low amyloid and relatively low normative blood perfusion values included parahippocampal and ambient gyri, orbito-frontal cortex (OFC) anterior orbital gyrus, OFC lateral orbital gyrus, anterior temporal lobe medial, and anterior temporal lobe (inferior and lateral).

Discussion

The findings of a spatial relationship between perfusion patterns in younger persons and amyloid deposition in late life are consistent with the hypothesis that high metabolic demands throughout life promote Alzheimer's pathology (Vlassenko et al., 2010). The distribution of aerobic glycolysis, the metabolic pathway of converting glucose into pyruvate, in normal young adults is spatially and positively correlated with Aβ deposition in Alzheimer's disease patients and healthy elderly controls with elevated Aβ (Vlassenko et al., 2010). As glucose metabolism and blood perfusion are tightly linked and to an extent proxies of each other (Fox & Raichle, 1986; Newberg et al., 2005; Paulson, Hasselbalch, Rostrup, Knudsen, & Pelligrino, 2010), our findings add to a growing body of work that implicates increased metabolism in early life to the development of Alzheimer's pathology in later life (Jagust & Mormino, 2011; Vlassenko et al., 2010). Glucose and oxygen, necessary for neuronal functioning, are delivered to neurons via astrocytes, which also regulate vasodilation and hence blood flow locally (Welberg, 2009), in line with the non-uniform Aβ deposition.

Our observation of the distribution of Aβ (Figure 2) is similar to described patterns of amyloid pathology (Thal et al., 2002), with cuneus, lingual gyrus, and insula showing higher relative levels of Aβ.

Although underlying mechanisms are unknown, elevated synaptic activity increases Aβ levels in the interstitial fluid of the brain and vesicle exocytosis, providing further evidence that metabolism may modulate region-specific Aβ (Bero et al., 2011). In transgenic Alzheimer's disease mouse models, endogenous neuronal activity regulates the regional concentration of interstitial fluid Aβ, which drives local Aβ aggregation (Bero et al., 2011). These previous observations emphasize again that neuronal activity affects amyloid deposition and that metabolism and blood perfusion are potential mediators of Aβ deposition within specific brain regions. However, compared with previous findings that focused on metabolism, blood perfusion levels imply additional mechanical and physical factors such as blood pressure, vasodilation/constriction, blood viscosity and hemodynamics that could lead to regional vulnerability for pathology over long periods of time. Our findings suggest that areas with relatively high blood flow throughout life are ultimately more susceptible to amyloid deposition, indicating that previously reported decreases in blood flow related to amyloid are either the result of the amyloid deposition, or acute changes that occur immediately prior to deposition of amyloid.

Acknowledgements

We thank all subjects for their study participation. We thank Daniel Summermatter from Division of Psychiatry Research and Psychogeriatric Medicine, University of Zuerich, Switzerland, for help in setup and administration of neuropsychological tests. There are no conflicts of interest pertaining to this publication for any of the authors involved.

Funding

This work was funded by the Swiss National Foundation (Schweizerischer Nationalfonds, SNF) grants 320030_125378/1 and 33CM30_124111 (to AFG) and Synapsis Foundation and Velux Foundation (to IBM), and received institutional support from the Division of Psychiatry Research and Psychogeriatric Medicine, University of Zürich and Institute for Biomedical Engineering University of Zürich and ETH Zürich, Switzerland.

9 General discussion

Taken together, we investigated how markers of vascular disease in healthy older adults contribute to cognitive decline, whether high field strength imaging is a useful tool for detecting such markers, and how normative metabolism is related to increased AD pathology later in life. In the introduction, we broached the issue of the presence of amyloid together with tau seeming to be necessary, yet not sufficient to explain the onset of AD alone. With the presented studies, mainly on the example of cerebral lobar microbleeds, as they reflect both vascular pathology *and* vascular forms of AD pathology (i.e., amyloid angiopathy), we provided evidence that vascular factors play a crucial role in the pathogenesis of AD, are among the earliest and most reliably detectable markers, and hence argue that they deserve more attention in research as well as clinical diagnostic processes than they currently do.

9.1 Findings and regional specificity of vascular damage

In both, our first and our second study, we found a negative relationship between presence of lobar microbleeds and executive functioning, which was to be expected based on the literature: In our first study, we observed that subjects with 2 or more lobar microbleeds had an accelerated rate of speed/executive function decline over a 9-year period preceding the MRI scan compared to subjects that had less than 2 microbleeds. In addition to previous studies, we added a longitudinal perspective and examined neurologically healthy older adults, further supporting the idea that executive functioning may be a primary target of vascular pathology and early cognitive changes.

Our second study was novel in as we used high magnetic field strength 7T MRI to establish a relationship between microbleeds and cognition, and thereby is a useful tool in microbleeds detection through its increased sensitivity. Our findings showed that microbleeds harbor clinically important information, as our subjects were relatively young and healthy, underpinning the previous observation of that executive functioning is a manifestation of cerebrovascular disease. An interesting observation of the study was the exclusively frontal and parietal distribution of microbleeds, which reminds us of the regional vulnerability of the brain vascular system depicted in the introduction (Chapter 5.3.2, WMH). However, we did not have enough statistical power for further analyses related to microbleed location. One of the biggest issues of the study was the small sample size of N=15, which we overcame by permutation tests for randomization, assigning subjects randomly 10'000 times to the microbleed versus no microbleed group, regardless of their status, to achieve the probability of finding the same value as the t-test between the two groups. As

the permutation yielded a very similar value, we concluded that group differences were very improbable to be due to chance.

In our third study, we found that microbleeds are associated with higher WMH burden overall and in particular in frontal and parietal regions, and that the presence of microbleeds leads to a more severe increase of WMH burden over time. We established that different vascular markers interact with each other or may in fact reflect the same underlying pathology, suggesting that small vessel cerebrovascular disease mediate the pathogenesis of AD. Our findings confirm our hypothesis, as both markers share the association with traditional vascular risk factors such as heart disease, obesity, diabetes, and hypertension, and further intensify the role of the vasculature, particularly in parietal brain regions, in conjunction with Alzheimer's disease (Brickman et al., 2008; Dufouil et al., 2001).

The reason for the vulnerability of frontal and particularly parietal lobes is mostly unclear, and its role in the pathogenesis of AD mostly underrepresented. While traditional radiological markers of neurodegeneration such as cortical thickness or hippocampal atrophy do have a good predictive value of structural measures in AD, metabolic imaging results are slowly shifting the focus towards the posterior association areas, clearly indicating an involvement in the early stage of the disease (Woodard et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008; Jagust et al., 2009; McDonald et al., 2009; Stricker et al., 2009) In the following, we will discuss four possible reasons for parietal lobe 'frailty', all of which are ultimately related to underlying vascular and/or metabolic processes, and how they could relate to cognitive aging and AD:

First, parietal lobes are considered a cognitive multimodal region, including many functions such as attention, mental rotation, calculation, spatial working memory, and even executive functions and episodic memory (Husain & Nachev, 2007; Jacobs, Van Boxtel, Jolles, Verhey, & Uylings, 2012), and are anatomically closely linked to the medial temporal areas associated with memory functions (Kobayashi & Amaral, 2003, 2007). Multimodal regions further tend to have high synaptic complexity and energy requirements, putting an additional strain on neuronal functioning and hence rendering them more vulnerable to stress and damage (Bruner, de la Cuetara, Masters, Amano, & Ogihara, 2014). Alternatively, the disruption in parietal lobe could also be affecting key pathways connecting frontal and parietal lobes, which are known to be involved with executive functioning/working memory (Brickman et al., 2009).

Second, our species might undergo additional stress in terms of energy balance due to the delay in brain growth and development, which could further increase vulnerability to metabolic failures (Bufill, Blesa, & Augusti, 2013). The increase of parietal volumes and surface in humans compared to their antecedents is assumed to be related to increase in metabolic and thermal loadings from additional brain fibers (Karbowski, 2009; Sukstanskii & Yablonskiy, 2006; Yablonskiy, Ackerman, & Raichle, 2000). Fiber-specific properties also seem to play a role for their development, metabolic demand, and susceptibility to AD pathology (Bartzokis, 2011; Bartzokis, 2009; Bartzokis, Lu, & Mintz, 2007; Braak, Del Tredici, Schultz, & Braak, 2000; Reisberg et al., 1999).

Third, one of the main reasons for the vascular vulnerability of parietal lobes is their localization at the end of the boundaries of the three major cerebral arteries, known as the watershed areas, the border zone between vascular territories with no or little anastomosis causing poorer local perfusion (Momjian-Mayor & Baron, 2005). The evolutionary increased vascular coverage of parietal lobes and the fact that vascular impairments disturb amyloid clearance may be an explanation for why amyloid accumulation starts in the neocortex. Furthermore, the anatomical proximity as well as integrative connections of the parietal lobes with its neighboring areas explains why clinical consequences of parietal lobe pathology are complex due to their underlying interconnected system, rather than showing isolated effects.

A fourth and more unexplored reason for the observed vulnerability could be the anatomical location of parietal lobes in relation to gravity. Vascular pressure, made up of viscous flow pressure pumping against the resistance of vessels, and pressure caused by gravity, called hydrostatics, must be overcome to reach a location of higher level of gravitational potential energy (Badeer, 1986), which in frontal and even more so parietal lobes is higher than in the other lobes. The vascular architecture of the human brain reveals a disproportionate distribution of vertically/upward-oriented vessels in those two areas, compared to a larger proportion of horizontally or downward projecting vessels in the other brain regions. It is possible that this distribution of vessel orientation results in differential perfusion patterns or energetic expenditure due to different responses of gravity on blood flow (Seymour, Hargens, & Pedley, 1993), rendering frontal and parietal lobes more vulnerable to vascular injury. Evidence about increased sensitivity to blood pressure variability in areas of mainly vertical vessels (frontal and parietal lobes) (Brickman et al., 2010) supports the argument that it is likely that the orientation of vessels has differential responses to the hemodynamic of the given areas, and that perfusion of 'vertical' vessels is more susceptible to blood pressure variability than perfusion of 'horizontal' vessels.

Taken together, the increase of brain mass, metabolic activity, anatomical changes, and changes in vascularization of the modern human brain may account for our higher cognitive functions, but its expenditure comes at the cost of increased vulnerability to stress, pathology, neurodegeneration, and ultimately dementia, and a particular regional vulnerability of the vascular system.

9.2 Cerebral blood perfusion and amyloid

In line with the hypothesis of increased metabolic demand of higher cognitive functioning areas, our fourth study examined regions of normative cerebral blood perfusion from healthy, younger adults and their relationship with Aβ deposition later on, and found a spatial correlation between the two, indicating that these regions are at a particular risk for the development of AD pathology. These findings are in line with a growing body of literature (Jagust & Mormino, 2011; Vlassenko et al., 2010), suggesting that mere mechanical and physical factors such as blood perfusion and composition, as well as hemodynamics that are non-pathological *per se* could have an impact on the development of AD, which leads to the conclusion that AD may in fact be a sort of developmental disorder, in which spatial variability in blood perfusion may promote pathology in late life.

Although we observed normatively increased regional metabolism and blood perfusion in younger adults related to Aβ deposition later on, it is unsurprising that cross-sectional studies (Cselenyi & Farde, 2015; Mattsson et al., 2014; McDade et al., 2014) show reduced regional blood flow in areas of Aβ deposition due to age-related vascular pathology. Mouse models evidence the vasoactive effects of Aβ once it is present (Crawford et al., 1998), and therefore support the argument of a direct relationship between amyloid and blood flow, suggesting that soluble Aβ may exert deleterious effects on vasculature and that progressively evolving cerebral circulatory abnormalities could further contribute to AD pathogenesis (Beckmann et al., 2003). The influence of Aβ in cells of vasculature disrupting the vascular tone may be a pathogenic factor in the development of CAA (Crawford et al., 1998). The resulting ischemia is assumed to upregulate βAPP production in and around the vasculature, further increasing Aβ formation and aggregation, with the final stage of vessels destruction and neuronal degeneration. The presence of CAA was also found to reduce regional cerebral blood flow in transgenic mouse models (Maier et al., 2014) as well as humans (Peca et al., 2013; Thal et al., 2009), connecting vascular amyloidosis to quantitative loss of perfusion.

While there are myriad other processes simultaneously involved and interacting in the aging brain, such as oxidative stress and inflammation causing neuronal and neurovascular dysfunction, myelin breakdown (Bennett, Grant, & Aldred, 2009; Iadecola, 2010), disconnection, and decreased Aβ clearance (Schreiber et al., 2014), aside from genetic and epigenetic mechanisms (Lahiri et al., 2016), we will focus our attention on current treatment approaches and how our findings could help develop further clinical trials and therapeutic interventions.

9.3 Current and possible future interventions in Alzheimer's disease

The majority of current AD trials focus on cerebral amyloid accumulation. Encouraging facts for such an approach stem from studies registering a 3 to 5-fold increased likelihood of progression to AD in case of positive markers (Brys et al., 2009; Forsberg et al., 2008; Hansson et al., 2006) (Mattsson et al., 2009; Vemuri et al., 2009; Visser et al., 2009) and greater risk of cognitive decline of amyloid-positive individuals (Fagan et al., 2007; G. Li et al., 2007; Morris et al., 2009; Rentz et al., 2010; Skoog et al., 2003; Villemagne et al., 2011). Hence, current trials mostly target amyloid, either by decreasing of Aβ production or aggregation, increasing of Aβ degradation or clearance, decreasing of tau and NFT formation, or by neuroprotection and/or neuroregeneration, such as anti-oxidants to preserve metabolic/mitochondrial functions, anti-aptoptotic agents, decrease of inflammatory damage, nerve growth factor enhancement, or stem-cell replacement (Sperling, Jack, et al., 2011).

However, long-term results and side effects of most current clinical trial studies are daunting, as most of them have not achieved the desired results (Doody et al., 2014; Salloway et al., 2014) (Feldman et al., 2007; Kadir et al., 2008; Schuff et al., 2011) and come at the cost of large side effects (Ostrowitzki et al., 2012; Salloway et al., 2014; Salloway et al., 2009). In the example of the earlier described Amyloid-Related Imaging Abnormalities (ARIA) in immunotherapeutic clinical trials, it is hypothesized that immunization may precipitate failure of perivascular Aβ mechanisms, and that usually soluble waste products like Aβ accumulate, modifying vascular permeability as well as leakage of plasma and blood products (Iliff et al., 2012). Future advances in microscopic *in vivo* techniques visualizing CAA in transgenic mice (Klohs, Rudin, Shimshek, & Beckmann, 2014) are necessary to help clarify how vasculopathy is temporally liked to vascular Aβ deposition or evaluate Aβ removal strategies.

Based on the unsuccessful Aβ-trial outcomes, the presented empirical evidence on the importance of cerebrovascular risk markers in the aging brain, and the classical vascular risk factors that are associated with disease pathogenesis and AD expression, we think that targeting the vascular system

may be an important, potent, and more promising medium for intervention. And while a number of failed approaches such as targeting vascular genotype status (Kennedy, Cutter, & Schneider, 2014) or vascular care of AD patients with cerebrovascular lesions (Richard, Kuiper, Dijkgraaf, Van Gool, & Evaluation of Vascular care in Alzheimer's, 2009) were reported, we believe that these interventions are favorable, but started too late in the disease process, once subjects had already received an AD diagnosis and exhibited symptoms. These results may also call for a more microbiological and molecular intervention of localized processes rather than focusing on traditional vascular risk factors. But it was not until 2014 that the National Institutes of Health (NIH) finally started using the term "vascular contributions to cognitive impairment and dementia", recognizing the importance of vascular factors, whose scope includes the neurovascular unit, infarcts, AD biology, metabolic disease, and immune stressors (Corriveau et al., 2016) giving rise to new disease-modifying approaches in AD.

Evidence from mouse studies shows how breakdown of cerebral blood vessels, or more specifically pericytes, can cause or exacerbate AD-related pathology and may provide a better understanding of the overlap between AD and vascular dementia (Sagare et al., 2013). Pericytes surround the outside of blood vessels and form part of the blood-brain-barrier (BBB), controlling movement of cells and molecules between the blood and the interstitial fluid of neurons, and help transport nutrients as well as waste molecules. In the study, genetically engineered mice with fewer pericytes than normal, decreased brain blood flow, and damage to the blood-brain-barrier, had enhanced learning and memory problems as well as increased Aβ plaque deposition near brain cells and along blood vessels compared to their APP-mutant counterparts, but also enhanced neuronal cell death and tangle formation in the hippocampus and the cortex, reflecting sporadic AD pathology. The study further showed that Aβ enhances vascular damage (also: (Arrighi, 2016) and leads to pericyte death, suggesting that toxic effects of increases Aβ deposition in cerebral blood vessels of older individuals causes blood-brain-barrier breakdown and impairs the ability of amyloid clearance, while the process occurs years prior to symptom onset (Skoog, 1997). Simultaneously, increased Aβ aggregation and the death of pericytes feeds back to aggravate the system and eventually leads to cell death, neuronal atrophy, and dementia. Furthermore, ApoE4 genotype related to AD renders the BBB more porous (Bell, 2012), which may allow circulating amyloid-beta peptides to cross it and, at least in aged monkeys, contributes to AD lesions (Mackic et al., 2002). Hence, pericytes and the blood-brain-barrier could be an interesting target for clinical trials in AD.

An alternative idea could be weakness of aging vessels due to lifelong exposure of vascular risk factors, and more so small vessels given their increased vulnerability, leading to spontaneous

ischemic and hemorrhagic infarcts reflected as lacunar strokes and microbleeds. The damage in the vessel walls may disrupt regional blood flow (Maier et al., 2014) as well as the blood-brain-barrier, supposed to act as a defense-system for the brain, and facilitate aggregation of toxic Aβ, which exacerbates the local damage itself. Secondary effects of the local damage, such as blood flow disturbances or hemosiderin deposition in the presence of microbleeds, that may put additional strain on the system causing oxidative stress and toxicity, may further weaken the vessels as well as the clearance system of the brain. Alternatively, endothelial injuries resulting from hypertension could first lead to multiple sites of blood brain barrier leakage, causing a weakening of the vessel wall and resulting in ruptures and microbleeds (Schreiber, Bueche, Garz, & Braun, 2013), then impair blood flow, and ultimately facilitate amyloid accumulation and toxicity. Prolonged inflammation and progressive white matter disease would be some of the consequence of the initial microvascular pathology starting the process, decreasing metabolism and cortical functions (Kuczynski et al., 2010). Either way, amyloid would act as a second, independent 'hit' on the system following vascular damage. These hypotheses could explain why amyloid is necessary, but not sufficient for an AD diagnosis, why some amyloid positive individuals show no AD-like symptoms, and why almost all AD cases have evidence of vascular damage and symptoms get aggravated and accelerated in its presence. We therefore conclude that treatment targeting amyloid may take action too late in the process, that vascular markers may be detected and treated earlier, and that they hence may be the more fruitful targets for disease modifying therapy in Alzheimer's disease.

9.4 Conclusion

At the current stage, there is not enough evidence to choose one of the suggested options in which vascular and amyloid pathology may interact. Findings like subjects with evidence of elevated blood pressure having greater WMH volumes at a given burden of amyloid (Scott et al., 2015), or cognitive normality in patients with only AD type pathology, but marked decline with concomitant cerebrovascular disease (Esiri et al., 1999), point at a synergistic interference (option B), but give no indication about the temporal ordering of events nor the magnitude of the individual pathological contributions. Nonetheless, it is fair to conclude that there exists an interdependency in various processes and at various stages of the disease pathogenesis, and it becomes clear that we are in need for further research, better instruments, more funds, and an open mind away from the dominating hypothesis that AD begins with the deposition of amyloid.

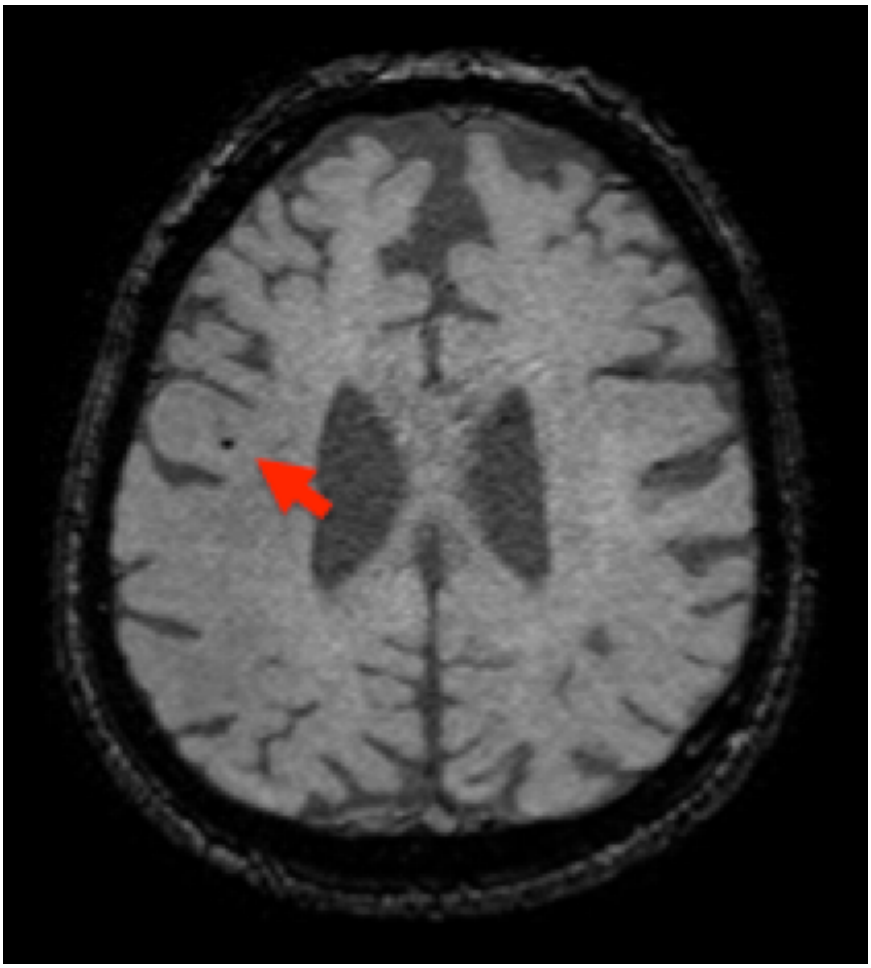
Until gaining more insight into the disease pathogenesis and more promising treatment outcomes, efforts such as a global health campaign could be highly valuable and relatively cost-effective. We

conclude that AD seems to be a developmental disorder, made up of life-long accumulation of different exposures to habits and risk factors summed up with the word 'aging', such as hypertension, diabetes, hypercholesterolemia, heart disease, smoking, alcohol. Further factors include normal spatial variability in blood flow, which is presumably non-pathological *per* se, as well as protective factors like exercise, a healthy diet, sleep, and many more. Taken together, those factors ultimately decide over 'normal cognitive aging versus AD'. Simply raising awareness about nutrition, exercise, smoking – all impacting vascular health and promoting AD – could lead to an enormous reduction of expenditures for the public health system, delay of disease onset, and hence relief of patients and care takers. Direct implications from our findings suggest taking into account the role of vascular disease and specifically lobar cerebral microbleeds for prognostic as well as diagnostic formulations.

10 Figures and Tables

10.1 Introduction, Chapter 3:

Figure 1: Cerebral local microbleed on 1.5T MRI



10.2 Study 1, Chapter 8.1:

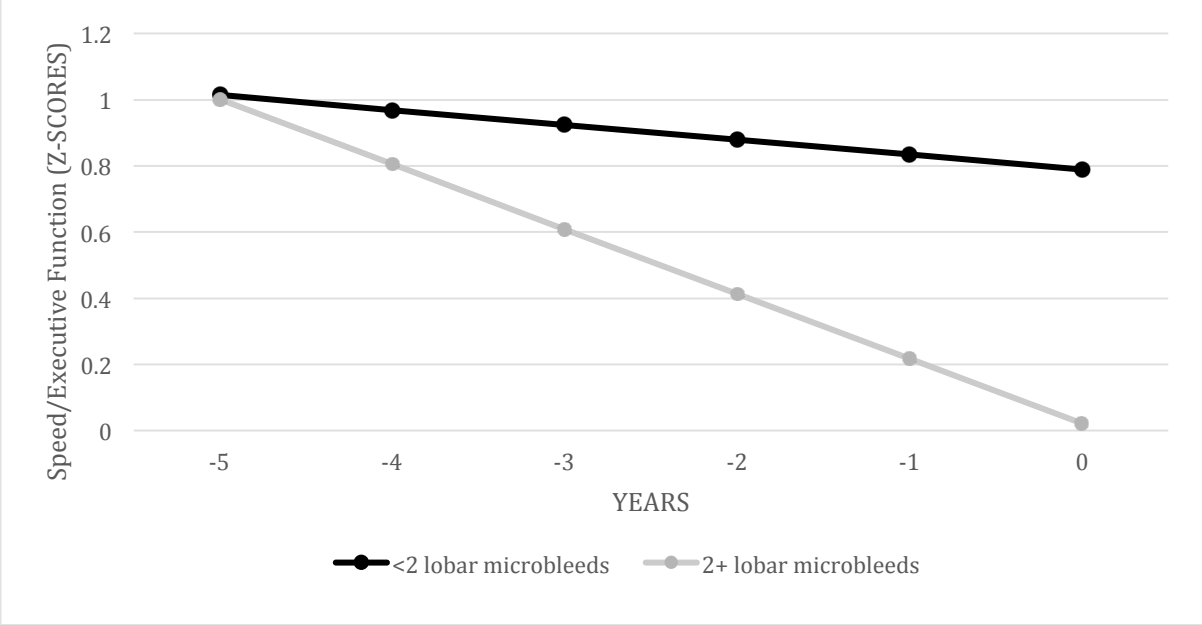
Table 1. Subject demographic data.

	<2 lobar microbleeds (n=186)	2+ lobar microbleeds (n=11)	Total Sample (n=197)	Statistic
Age at date of MRI scan	84.14 (+/-5.06)	84.39 (+/-4.44)	84.15 (+/-5.02)	t=0.619; p=0.871
Education (mean years +/- SD)	11.84 (+/-4.65)	10.00 (+/-6.73)	11.75 (+/-4.78)	t=1.190; p=0.235
Speed/Executive function at first visit (mean score +/- SD)	0.48 (+/-0.06)	0.19 (+/-0.51)	0.46 (+/-0.92)	t=0.965; p=0.336
Memory at first visit (mean score +/- SD)	0.54 (+/-0.58)	0.28 (+/-0.76)	0.53 (+/-0.59)	t=1.447; p=0.150
Language at first visit (mean score +/- SD)	0.49 (+/-0.55)	0.48 (+/-0.67)	0.49 (+/-0.55)	t=0.088; p=0.930
Visuospatial functioning at first visit (mean score +/- SD)	0.49 (+/-0.51)	0.38 (+/-0.66)	0.48 (+/-0.52)	t=0.699; p=0.485
Sex (% women)	68.2	60.0	67.52	X^2=0.517; p=0.350
Ethnicity (%African American/Hispanic/White)	34/27/39	46/33/21	35/29/36	X^2=1.992; p=0.369

Table 2. GEE analyses for the domains speed, memory, language, and visuospatial functioning. Beta values are standardized.

VARIABLE	SPEED/EXECUTIVE FUNCTION		MEMORY		LANGUAGE		VISUOSPATIAL	
	b	p	b	p	b	p	b	p
Group (0= < 2 microbleeds, 1= 2+ microbleeds)	-0.392	0.108	0.122	0.307	-0.055	0.660	0.001	0.857
Time	-0.044	<0.001	-0.028	<0.001	-0.010	0.003	-0.061	0.699
GroupXTime	-0.072	0.012	0.016	0.288	-0.005	0.793	0.026	0.137
Age	-0.013	0.013	-0.014	0.002	-0.010	0.001	-0.007	0.009
Sex (0=M, 1=F)	-0.006	0.912	0.097	0.050	0.047	0.113	0.057	0.039
Education	0.017	0.019	0.015	0.024	0.014	0.019	0.021	<0.001
Baseline cognition	0.774	<0.001	0.726	<0.001	0.804	<0.001	0.686	<0.001

Figure 1. Differential decline in speed/executive functioning among individuals with 2 or more microbleeds versus controls. Caption: Plotted results of GEE model examining the Group x Time interaction for the cognitive domain of Speed/executive function, adjusted for age, education, ethnicity, sex, and cognitive performance at first visit. The MRI scan for microbleed assessment was completed at Year 0.



10.3 Study 2, Chapter 8.2:

Figure 1. 7 Tesla T2*-gradient echo (GRE) scans of cerebral lobar microbleeds (frontal lobe): axial, coronal, and sagittal view

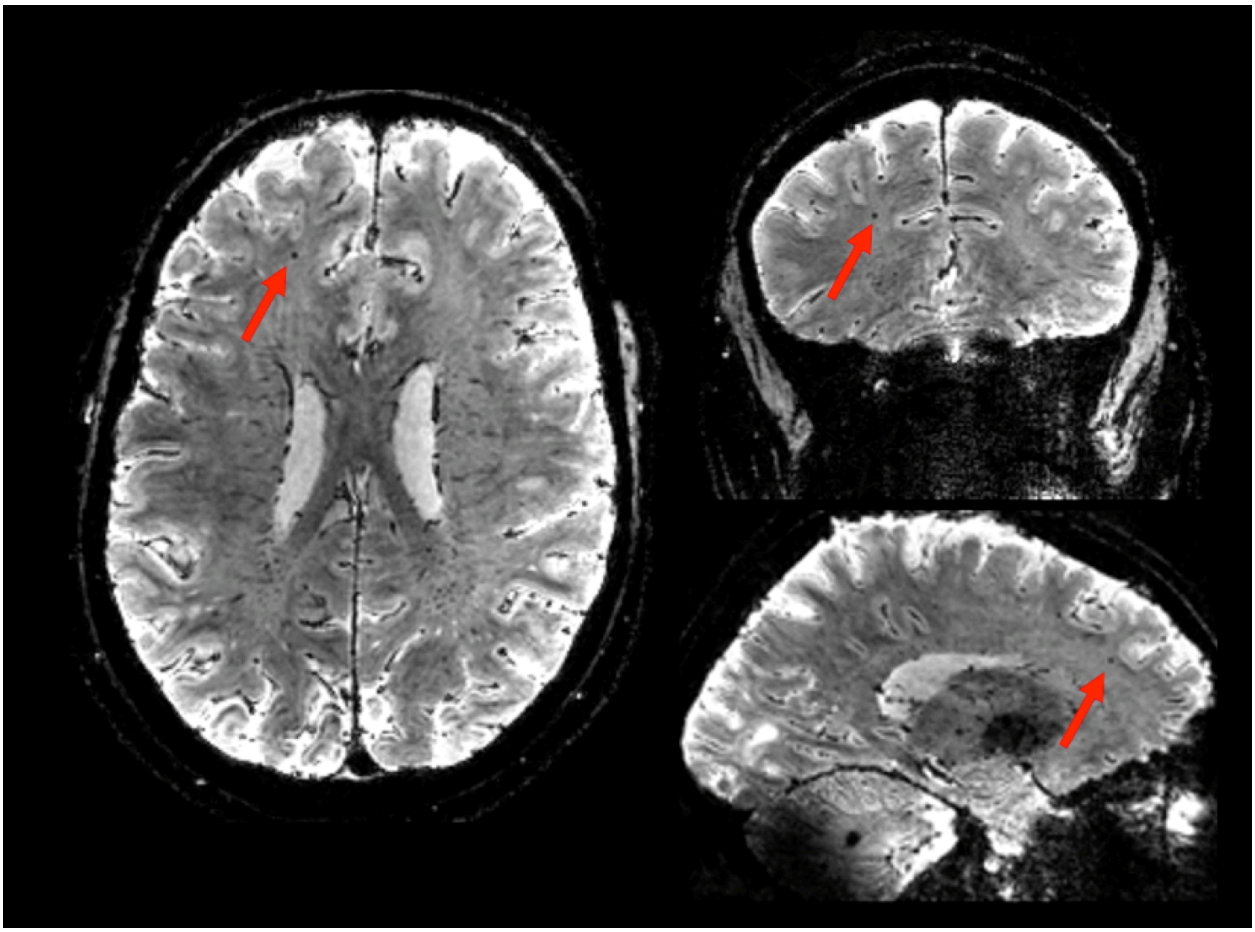


Table 1. Subject demographics: age, education, and sex for subjects with and without lobar microbleeds (MB).

	No lobar MB (n=10)	Any lobar MB (n=5)	Total Sample (n=15)	Statistic
Age	69.10 (+/-6.17)	66.60 (+/-1.34)	68.27 (+/-5.15)	t=.0882; p=0.395
Education (mean yrs +/- SD)	15.10 (+/-2.42)	14.20 (+/-1.30)	14.80 (+/-2.11)	t=0.767; p=0.457
Sex (% women)	4 (27%)	3 (20%)	7 (47%)	t=0.536; p=0.464

Table 2. Differences in cognitive test performance between individuals with no microbleeds (MB) and those with any microbleeds. Scores are reported as means and standard deviations, significant findings are indicated in bold.

DOMAIN	VARIABLE	No MB	Any MB	t	p
Attention	Trail Making Test A, time to completion (seconds)	39.20 (10.55)	38.00 (12.00)	0.199	0.845
	Digit Span Forward, number of correct items	7.40 (0.97)	7.60 (1.34)	0.333	0.744
Memory/Learning	List Learning Immediate Recall (VLMT), number of correct items	10.80 (2.35)	12.60 (1.51)	1.545	0.146
	Rey Delayed Recall, number of correct items	21.55 (3.91)	23.30 (2.38)	0.909	0.380
Language	Letter Fluency, number of words generated in 60 seconds	24.70 (5.93)	23.60 (4.83)	0.358	0.726
	Boston Naming, number of correct items	14.70 (0.67)	14.80 (0.45)	0.297	0.771
Visuospatial/Executive Functioning	Trail Making Test B, time to completion (seconds)	88.50 (25.56)	69.00 (12.59)	1.590	0.136
	Rey Copy, number of correct items	**33.75 (1.78)**	**31.00 (2.55)**	**2.449**	**.029***
Global Cognition	MMSE	29.3 (1.06)	29.8 (0.45)	0.997	0.337

10.4 Study 3, Chapter 8.3:

Table 1. Subject demographic data

	no lobar microbleeds (n=148)	any lobar microbleeds (n=39)	Total Sample (n=187)	Statistic
Age at evaluation	85.59 (+/-5.11)	85.33 (+/-5.21)	85.48 (+/-5.12)	t=0.028; p=0.75
Sex (% women)	108 (73)	27 (69.2)	135 (72.1)	X^2=0.22; p=0.64
Ethnicity (%African American/Hispanic/White)	34/37/29	46/31/23	37/35/28	X^2=2.86; p=0.41

Figure 1. Mean WMH volume for four lobes in subjects with and without lobar microbleeds (cross-sectionally, MRI at Time 2). F(3, 519)=9.82; p<0.001

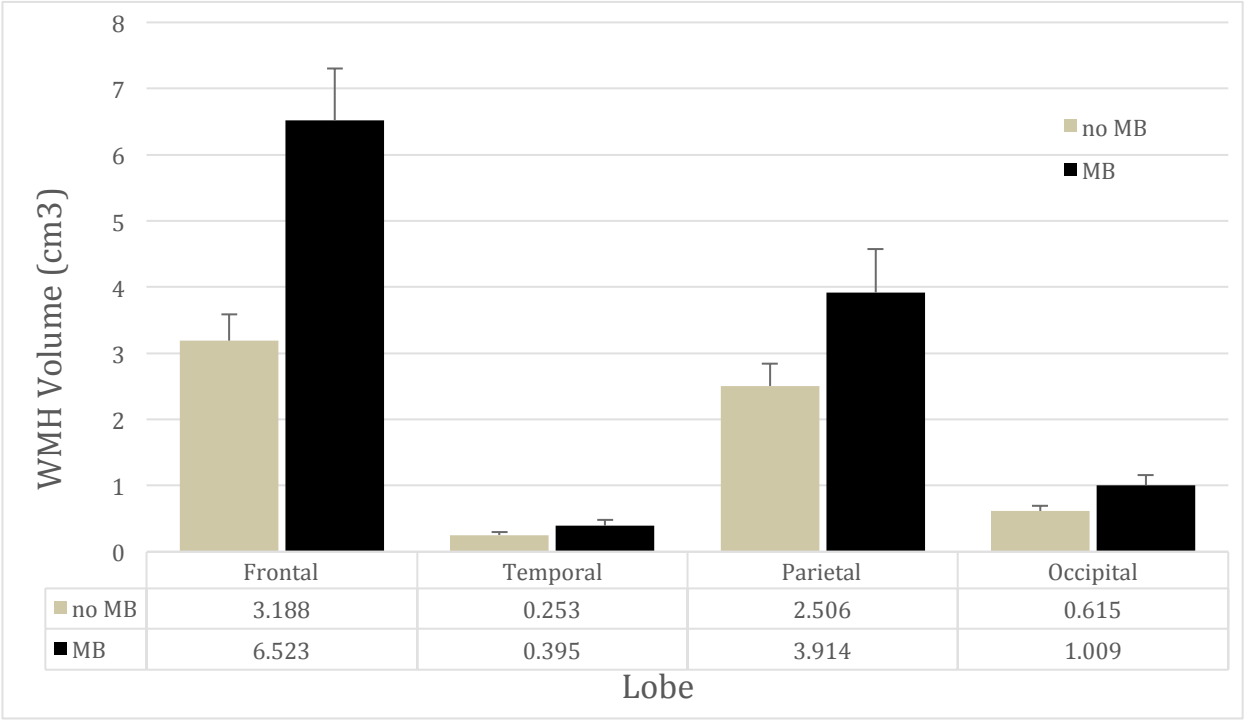
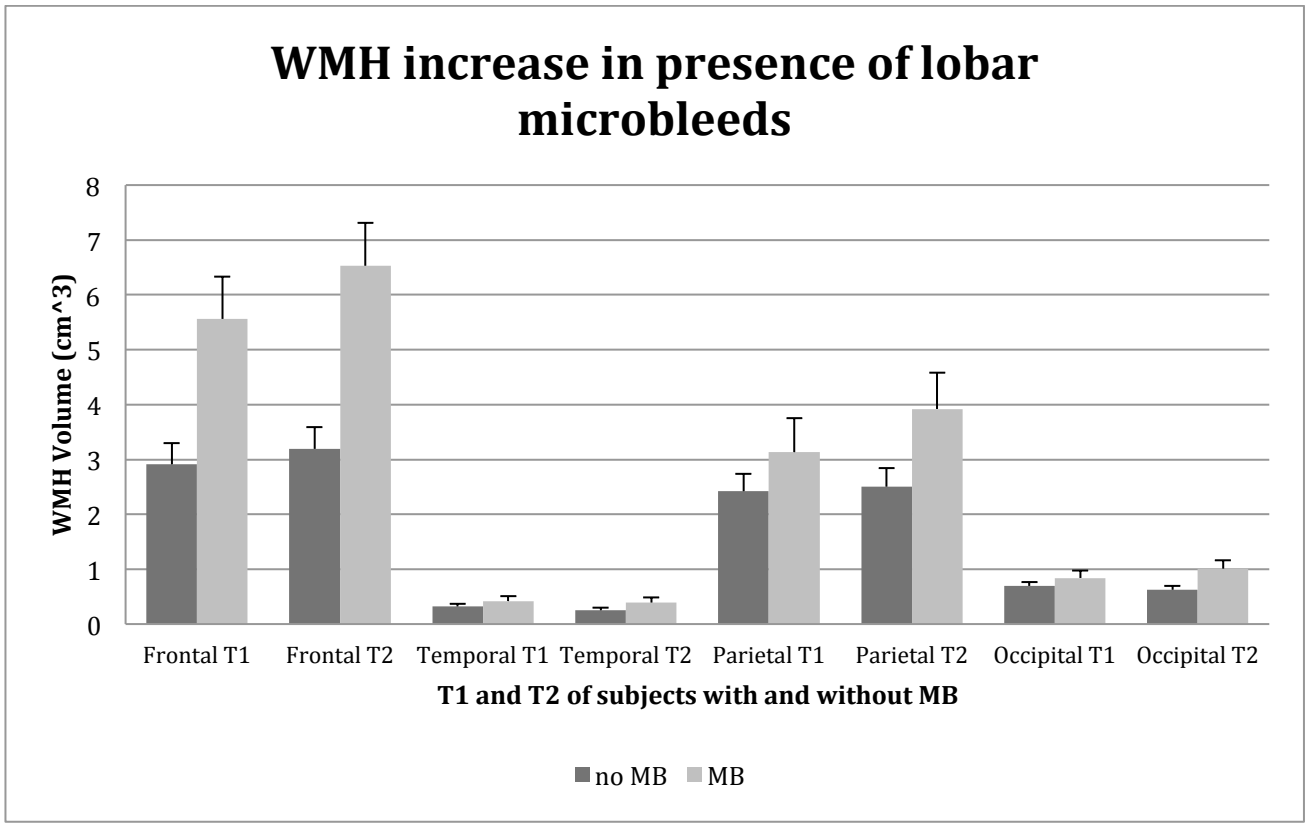


Figure 2. Mean WMH volume increase for four lobes in subjects with and without lobar microbleeds (longitudinally, T1 to T2).



10.5 Study 4, Chapter 8.4:

Figure 1. Spatial correlation between blood perfusion in younger adults and Aβ deposition in older adults. The figure displays mean blood perfusion values in each ROI (grey bars) and corresponding PiB SUVR values (dotted lines). The ROIs are rank ordered from highest to lowest PiB SUVR values.

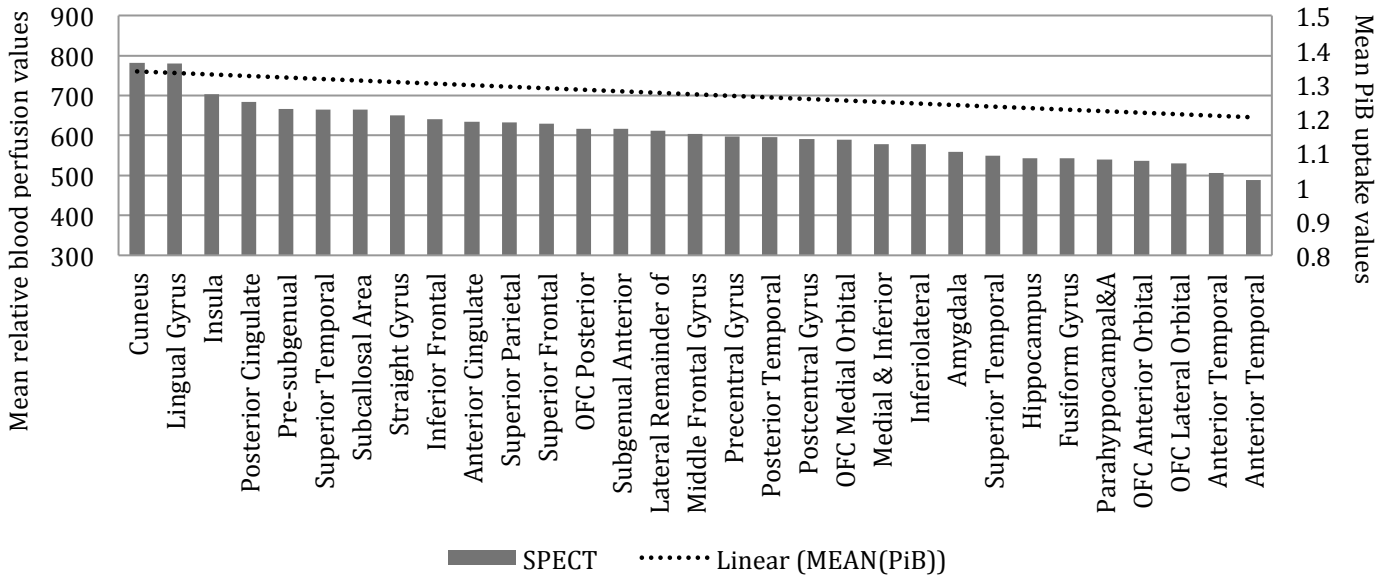


Figure 2. Blood flow quartiles in association with Aβ deposition. Mean PiB SUVR values in older adults in regions defined by perfusion values in younger adults. Error bars are standard deviations.

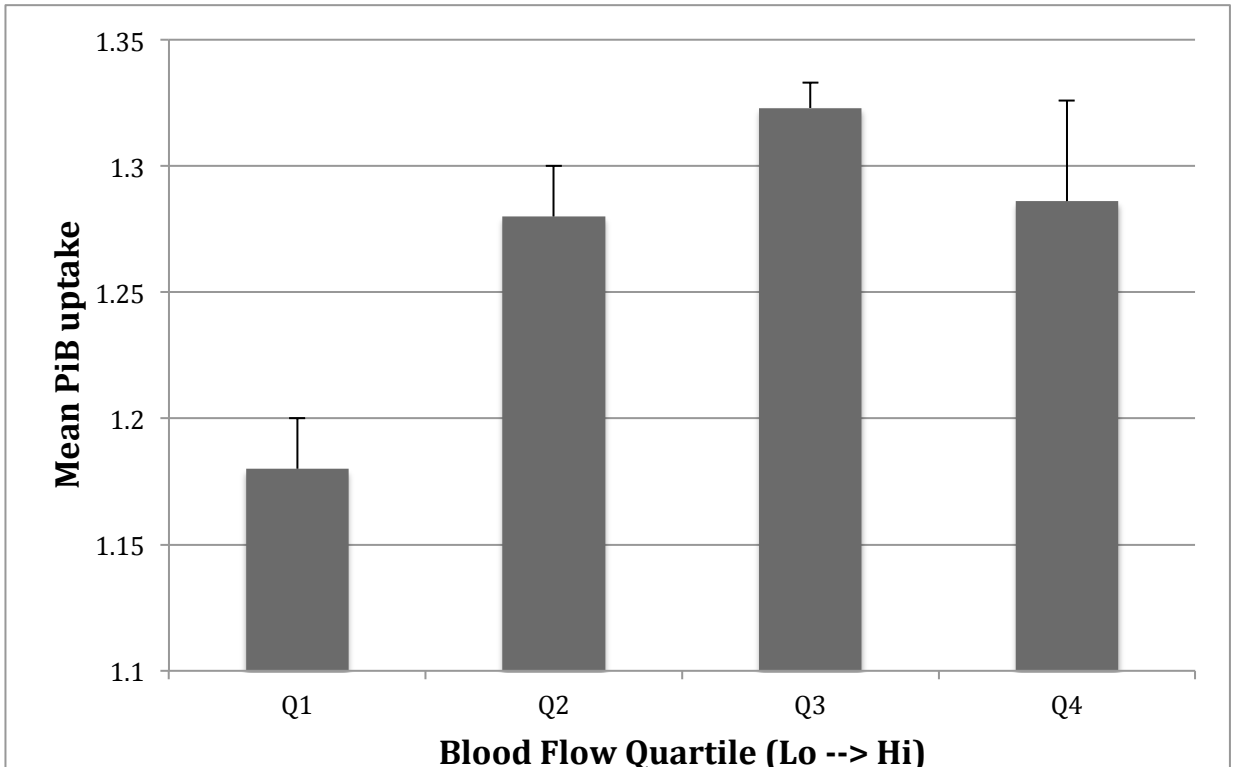
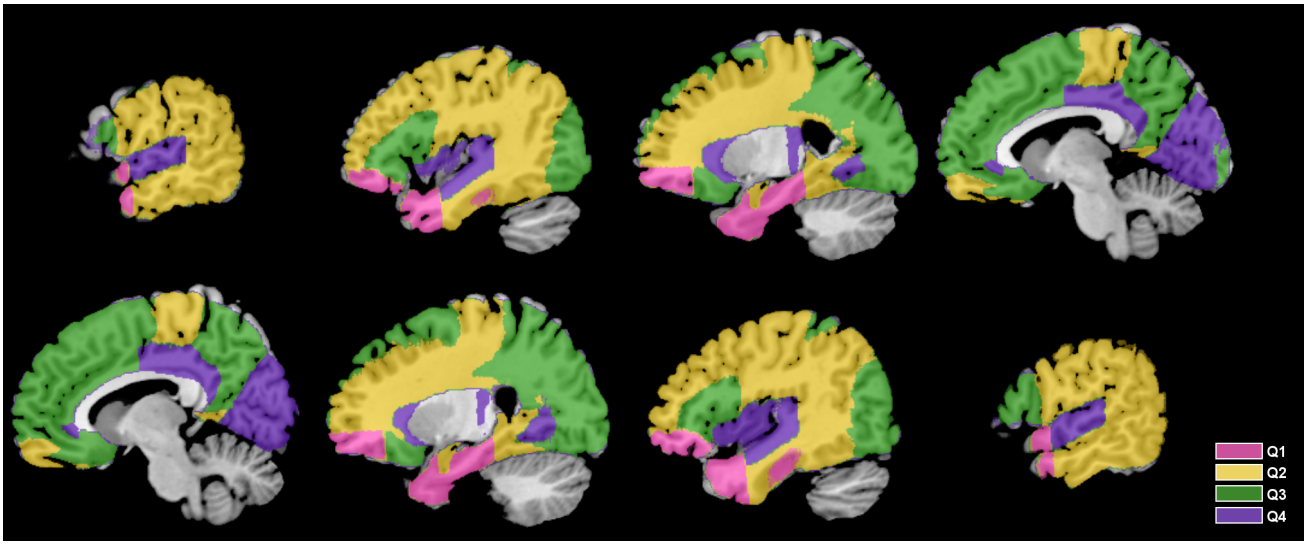


Figure 3. Spatial distribution of amyloid deposition as a function of normative regional blood perfusion. Regions-of-interest were rank ordered from lowest to highest based on relative perfusion values in younger adults and then divided into four quartiles. Quartile 1 (Q1, pink) includes anterior temporal lobe inferior and lateral, anterior temporal lobe medial, lateral orbital gyrus, anterior orbital gyrus, parahippocampal and ambient gyri, fusiform gyrus, and hippocampus. Quartile 2 (Q2, yellow) includes superior temporal gyrus (anterior), amygdala, inferiolateral remainder of parietal lobe, medial & inferior temporal gyrus, medial orbital gyrus, postcentral gyrus, posterior temporal lobe, precentral gyrus. Quartile 3 (Q3, green) includes middle frontal gyrus, lateral remainder of occipital lobe, subgenual frontal cortex, posterior orbital gyrus, superior frontal gyrus, superior parietal gyrus, anterior cingulate gyrus, and inferior frontal gyrus. Quartile 4 (Q4, purple) includes straight gyrus, subcallosal area, superior temporal gyrus (posterior), pre-subgenual frontal cortex, posterior cingulate, insula, lingual gyrus, and cuneus.



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12 CV

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Date of birth: October 8, 1986

Nationality: Swiss

Current Position

University of Zurich/Columbia University New York: PhD student of neuroscience.

Collaboration with the Psychological Institute and Center for Neuroscience (ZNZ) of University of Zurich, and the Taub Institute for Research on Alzheimer's disease and the Aging Brain, at Columbia University in New York City.

Supervisors: Prof. Drs. Christoph Hock and Mike Martin (University of Zurich), Dr. Adam M. Brickman (Columbia University), Dr. Paul Gerson Unschuld (University of Zurich).

Topic: Assessment of Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET)-derived neurodegenerative and cerebrovascular markers of Alzheimer's disease.

Education

02/2010 – 12/2011	**University of Zurich**, Master of Science in Cognitive Psychology and Neuropsycholgy. Final grade: 5.9 (GPA=3.95). 2 semesters at Columbia University, New York, NY.
	Final thesis: *White matter predictors of cognitive function in older adults*. Referent: Prof. Dr. Lutz Jaencke. Supervisor: Dr. Adam M. Brickman (Columbia University, New York).
	Grade of thesis: 6.0 (GPA=4.). Grade of final exam: 6.0 (GPA=4.0)
	Minor Subject: (Neuro-)Biology. Final grade: 5.7 (GPA=3.65)
10/2005 – 02/2010	**University of Zurich**, Bachelor of Science in Psychology.
	Final thesis: *Prosody – Music of Language*.
	Advisor: Dr. Martin Meyer.
	Grade of thesis: 5.0 (GPA=3.75)
	Minor subjects: 1. (Neuro-)Biology
	2. Spanish Literature

08/1999 – 09/2005 High school: **Literargymnasium Raemibuehl**, Zuerich.
Profile: Latin/Spanish

Awards and Prizes

2015 Swiss General Consulate, Rio de Janeiro: remuneration for exceptional and continuous contribution for project management.

2015 Best Talk Award of the 11th Winter Brain Symposium (PhD Students), Division of Psychiatry Research, UZH

2014 Vontobel-Preis fuer Alter(n)sforschung (Vontobel Award for Research on Age(ing))

Grants/Stipends/Fellowships

2015 ZNZ Travel Fellowship for the 2015 Alzheimer's Disease/Parkinson's Disease (AD/PD) Conference in Nice, France.

2014 Synapsis Foundation: 3-year fellowship and research stipend for PhD studies

2013 VELUX foundation: 3-year fellowship and research stipend for PhD studies

2012 Student Volunteer Travel Fellowship (full funding) for the 2012 Alzheimer's Association International Conference (AAIC) in Vancouver, British Columbia, Canada

2010 Gottfried und Julia Bangerter-Rhyner foundation for medical research: 2-year fellowship for classes

2009 Gottfried und Julia Bangerter-Rhyner foundation for medical research: fellowship and research stipend for research at Columbia University in New York

Work Experience

04/2015 – 12/2015 Scientific Advisor at swissnex Brazil, Rio de Janeiro (Project Management in the areas of sustainability, innovation/start ups, science)

03/2013 – 08/2013 Universidad Autónoma de Madrid (Spain): Visiting researcher. Conducting EEG experiments on automatic response to emotional stimuli. Mentor: Prof. Dr. Luis Carretié Arangüena.

06/2010 – 12/2012 Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York: Research Assistant. Mentor: Adam M. Brickman, Ph.D.

- Primary neuropsychological evaluator for studies investigating effects of exercise and dietary interventions on dentate gyrus functioning and cognition; patient testing, data management, preparation for analysis, cooperation with Behavioral Medicine group (Principle Investigators: Dr. Scott A. Small, Dr. Richard Sloan).
- Rating microbleeds on gradient echo (GRE) MRI sequences based on Boston Criteria (Dr. Steven M. Greenberg, Harvard).
- Evaluation of lacunar infarcts on T1-weighted and T2-weighted/FLAIR MRI sequences, measuring vascular parameters on T2-weighted images (Dr. Jose Gutierrez, Columbia University).
- Set up database and coordinate infarct rating group; data management.
- Manual labeling of regional white matter hyperintensities on FLAIR MRI sequence.

- Data collection at New York University in collaborative study (with Dr. Wendy Suzuki) of the impact of exercise on cognition, data management, and preparation for analysis.
- Manuscript preparation and statistical analysis for cortical thickness, white matter hyperintensity, and tract integrity studies (see 'Publications').

01/2010-06/2010	University of Zurich: 20% Assistant to Prof. Dr. Klaus Jonas (Director of the Psychology Department), chairman of Social Psychology (Psychological Institute, Universitaet Zurich, Binzmuehlestrasse 14, 8050 Zurich).
02/2010-05/2010	University of Zurich: 50% Practicum in Neuropsychology at the Geronto-Psychiatric University Clinic in Zurich (Minervastrasse 145, Postfach 1682, 8032 Zurich). Director: Prof. Dr. Christoph Hock, M.D.
02/2009; 08/2009	Assistant to Thomas Schwaller, preparing Swiss Matriculation Examination, State Secretariat for Education, Research, and Innovation SERI (Staatssekretariat für Bildung, Forschung und Innovation SBFI, Effingerstrasse 27, CH-3003 Bern).
08/2007; 08/2008	Assistant to Thomas Schwaller, preparing Swiss Matriculation Examination, State Secretariat for Education, Research, and Innovation SERI (Staatssekretariat für Bildung, Forschung und Innovation SBFI, Effingerstrasse 27, CH-3003 Bern).

Professional Memberships

2010 – present	International Society to Advance Alzheimer's Research and Treatment (ISTAART): Student member
2010 – present	International Neuropsychological Society (INS): Associate member

Training

11/2013	FreeSurfer Neuroimaging Course, Massachusetts General Hospital, Boston

Supplementary Activities

02/2014 – present	Chair of Student Liaison Committee (SLC) at *International Neuropsychological Society (INS).*
01/2013 – 02/2014	International Student Liaison Representative at *International Neuropsychological Society – Student Liaison Committee* (INS-SLC). Mentor: Dr. Robert Bilder, UCLA.
02/2013	Moderation of a panel session and presentation of board report at 'Board of Governor's' meeting as student liaison representative at *International Neuropsychological Society (INS)* in Waikoloa, Hawaii.
06/2010 – present	*Adhoc* journal review under supervision of Dr. A.M. Brickman: *Journal of the International Neuropsychological Society, Neurobiology of Aging, Human Brain Mapping, Current Alzheimer Research, Neurodegenerative Diseases.*
08/2012 – 12/2012	Harvard School of Public Health online class: *Health in Numbers: Quantitative Methods in Clinical & Public Health Research.*
08/2009 – 06/2010	During BSc: PhD tutorial courses at Neuroscience Center Zurich (ZNZ), with special approval from Prof. Dr. Martin Schwab: 1. *Introductory Course in Neuroscience* 2. *Neuroanatomy* 3. *Introduction into Technology and Assessment of Neuro MRI* 4. *Methodology of Functional MRI*

06/2010 – present	Attendance and participation in weekly neuropsychology group supervision for externs, clinical interns, and post-doctoral fellows at Columbia University, NY, with Drs. Adam Brickman, Jennifer Manly, and Stephanie Cosentino.
06/2010 – present	Regular observation of brain cuttings, Wada tests, weekly diagnostic consensus conferences and cognitive neuroscience seminars, monthly clinical pathological conferences. Regularly attend neurology and psychiatry grand rounds, clinical shadowing of neurologists, and attend stroke rounds at Columbia University, NY.
02/2008 – 09/2011	Advertisement for the department student psychology magazine 'aware' and regular composition of scientific articles currently discussed in the literature and in line with our study framework
02/2015 – present	Regional Director *Latin America* for *Sciencematters*: https://sciencematters.io/

Languages

Swiss German	Native language
German	Official language
English	Fluent: spoken and written. TOEFL scores: 111/120 (autodidactic)
Spanish	Fluent: spoken and written. 03/2013-08/2013: Visiting researcher at Universidad Autónoma de Madrid (Mentor: Prof. Dr. Luis Carretié Arangüena)
Portuguese	Fluent: spoken and written. 12/2012-02/2013: Studying Brazilian Language and Culture at 'Casa do Caminho' in Rio de Janeiro (BR); weekly private classes 03/ 2013-12/2014
French	Proficient: spoken and written. Diploma of Advanced French Language (DALF) 09/2008: Level C1 (5 out of 6); Scores: 68.5/100 (autodidactic) 06/2008-09/2008: Studying French Language and Culture at Sorbonne University, Paris

Neuropsychological Test Experience

- CERAD battery, MMSE, writing test reports and giving patient feedback (in German)
- Paper-pencil tests: Letter and Category Fluency, Stroop Test, Digit Symbol, Rey Auditory Verbal Learning Test (in English and Spanish); WAIS-IV, CVLT, WTAR, Rey-Osterrieth Complex Figure, Boston Naming Test, Tower of London Test, Trail Making Test, Wisconsin Card Sorting Test, Clock Test, Apraxia Testing, Digit Span Test, Logical Memory Test, Geriatric Depression Scale, Cumulative Illness Rating Scale
- Computer tests: CogState battery, ModBent, Craig Stark Task

Invited Conferences

- XIV Congress of the Brazilian Neuropsychology Society (Nov 21, 2015): (Conference Talk): "Cerebrovascular Risk Factors in Aging and Alzheimer's Disease"
- XIV Congress of the Brazilian Neuropsychology Society (Nov 21, 2015): (Round Table Moderation): "Neuropsychology and its applicability in different areas"

Personal Interests

- Long distance running (Greifensee Half Marathon, 2009; Staten Island Half Marathon, 2012; Philadelphia Marathon, 2012; Rock n' Roll Madrid Half Marathon, 2013; Grete's Great Gallop Half Marathon, NYC, 2013; ING New York City Marathon, 2013; JackRabbit Indoor Triathlon, NYC, 2014; Women's Half Marathon, NYC, 2014; Brooklyn Half Marathon, NYC, 2014; Grete's Great

Gallop Half Marathon, NYC, 2014; TCS New York City Marathon, 2014 [charity for "Alzheimer's Association"]; Revezamento das Praias, Half Marathon in sand, Rio de Janeiro, 2015; International Half Marathon of Rio de Janeiro, 2015).

- Open Water Diving
- Traveling and short term exchanges (Paris, Madrid, Malaga, Rio de Janeiro)

New York, 05/04/16

APPENDIX

Publications

Peer-reviewed articles

- **Meier, I.B**., A. Gietl, M. Wyss, S. Schreiner, S. Steininger, E. Gruber, S. Leh-Seal, A. Buck, A. Brickmann, R. M. Nitsch, K. Prüssmann, C. Hock, P.G. Unschuld (in submission). Lobar microbleeds are associated with executive functioning in healthy older adults: A 7T MRI study.
- **Meier, I.B.**, Gietl, A., Vorburger, R.S., Gutierrez, J., Holland, C., Guttmann, C.R.G., Meier, D., Nitsch, R.M., Hock, C., Unschuld, P.G., & Brickman, A.M. (in submission). Brain areas with normatively increased blood flow are more susceptible to amyloid deposition.
- **Meier, I.B.**, Guzman, V.A., Wiegman, A.F., Narkhede, A., Schupf, N., Manly, J.H., Luchsinger, J.A., Viswanathan, A., Martinez-Ramirez, S., Greenberg, S.M., Mayeux, R., & Brickman, A.M. (in preparation). Lobar microbleeds are associated with white matter hyperintensities.
- S.J. Schreiner, T. Kirchner, M. Wyss, J.M.G. Van Bergen, F.C. Quevenco, S.C. Steininger, E.Y. Griffith, **I.B. Meier**, L. Michels, A. Gietl, S.E. Leh, A.M. Brickman, C. Hock, R.M. Nitsch, K.P. Pruessmann4 A. Henning4, P.G. Unschuld (in submission). Low episodic memory test performance in cognitively normal elderly subjects is associated with increased posterior cingulate gray matter N-acetyl-aspartate: A 1H MRSI Study at 7 Tesla.
- Busovaca, E., Zimmerman, M.E., **Meier, I.B.,** Griffith, E.Y., Grieve, S.M., Korgaonkar, M.S., Williams, L.M., & Brickman, A.M. (2015). Is the Alzheimer's disease cortical thickness signature a biological marker for memory? *Brain Imaging and Behavior.*
- Brickman, A.M., Zahodne, L.B., Guzman, V.A., Narkhede, A., **Meier, I.B.**, Griffith, E.Y., Provenzano, F.A., Schupf, N., Manly, J.J., Stern, Y., Luchsinger, J.A., & Mayeux, R. (2015). Reconsidering harbingers of Alzheimer's disease: Regionally distributed progression of white matter hyperintensities in the community. *Neurobiology of Aging.*
- Schreiner, S.J., Liu, X., Gietl, A., Wyss, M., Steiniger, S., Gruber, E., Treyer, V., **Meier, I.B.**, Leh-Seal, S., Buck, A., Nitsch, R.M., Pruessmann, K.P., Hock, C., & Unschuld, P.G. (2014). Regional Fluild-Attenuated Inversion Recovery (FLAIR) at 7 Tesla is associated with Amyloid beta load in hippocampus and brain-stem of cognitively normal elderly subjects. *Front Aging Neurosci.*
- **Meier, I.B**, Gu, Y., Guzman, V.A., Wiegman, A.F., Schupf, N., Manly, J.J., Stern, Y., Luchsinger, J.A., Viswanathan, A., Martinez-Ramirez, S., Greenberg, S.M., Mayeux, R. & Brickman, A.M. (2014). Lobar microbleeds are associated with decline in executive functioning in older adults. *Cerebrovascular Diseases.*

- Wiegman A.F*, **Meier I.B.***, Provenzano F.A., Schupf N., Manly J.J., Stern Y., Luchsinger J., and Brickman A.M. (2014). Regional white matter hyperintensity volume and cognition predict death in a multi-ethnic, community cohort of older adults. *Journal of the American Geriatrics Society.* (*Authors contributed equally to this manuscript).

- Wiegman, A.F., **Meier I.B.**, Schupf N., Manly J.J., Guzman V.A., Narkhede A., Stern Y., Ramirez-Martinez S., Viswanathan A., Luchsinger J.A., Greenberg S.A., Mayeux R., and Brickman A.M. (2014). Cerebral microbleeds in the community: Demographic and clinical correlates. *Journal of the Neurological Sciences.*

- Brickman, A.B., **Meier, I.B.**, Wiegman, A., Guzman, V., Manly, J., Stern, Y., Luchsinger, J., Ramirez-Martinez, S., Viswanathan, A., Greenberg, S.E., Mayeux, R., & Schupf, N. (2013). Linking declining levels of plasma beta-amyloid 42 to Alzheimer's disease: The role of cerebral microbleeds. *The Journal of the Alzheimer's Association.*

- Provenzano, F.A., Muraskin, J., Narkhede, A., Wasserman, B.T., Griffith, E.Y., Guzman, V.A., **Meier, I.B.**, Zimmerman, M.E., & Brickman, A.M. (2013). White matter hyperintensities and cerebral amyloidosis: Necessary and sufficient for clinical expression of Alzheimer's disease? *JAMA Neurology.*

- **Meier, I.B.**, Manly, J.J., Provenzano, F.A., Louie, K., Wasserman, B.T., Hector, J., Allocco, E., and Brickman, A.M. (2012). White matter predictors of cognitive functioning among older adults. *Journal of the International Neuropsychological Society, 18,* 414–427.

- Brickman A.M., **Meier I.B.**, Korgaonkar M.S., Provenzano F.A., Grieve S.M., Siedlecki K.L., Wasserman B.T., Williams L.M., Zimmerman M.E. (2012). Testing the white matter retrogenesis hypothesis of cognitive aging. *Neurobiology of Aging, 33*, 1699-1715.

- **Meier I.B.**, Narkhede A., Provenzano F.A., Luchsinger J.A., Manly J.J., Willey J.Z., Viswanathan A., Martinez-Ramirez S., Greenberg S.M., and Brickman A.M. (2012). *Lobar microbleeds, white matter hyperintensities, and memory in older adults.* Manuscript in preparation.

Published Abstracts/ Presentations

- **Meier, I.B.**, Gietl, A., Vorburger, R.S., Gutierrez, J., Holland, C., Guttmann, C.R.G., Meier, D., Nitsch, R.M., Hock, C., Unschuld, P.G., & Brickman, A.M. (in submission). Brain areas with normatively increased blood flow are more susceptible to amyloid deposition.

- Schreiner, S.J.*, Liu, X.*, Gietl, A.F., Wyss, M., Steininger, S.C., Vanbergen, J., Treyer, V., **Meier, I.B.,** Leh, S.E., Buck, F., Nitsch, R., Pruessmann, K.P., Hock, C., & Unschuld, P.G. (in submission) Hippocampus and brainstem of cognitively normal elderly individuals show amyloid beta-associated tissue alterations as indicated by fluid-attenuated inversion recovery (FLAIR) MRI at 7 Tesla and 11C-PiB PET

- **Meier, I.B**., A. Gietl, M. Wyss, S. Schreiner, S. Steininger, E. Gruber, S. Leh-Seal, A. Buck, A.Brickmann, R. M. Nitsch, K. Prüssmann, C. Hock, P.G. Unschuld (2014, May). Lobar microbleeds are associated with executive functioning in healthy older adults: A 7T MRI study. *Society of Biological Psychiatry,* New York, NY.

- Schreiner, S.J., Liu, X., Gietl, A., Wyss, M., Steiniger, S., Gruber, E., Treyer, V., **Meier, I.B.**, Leh-Seal, S., Buck, A., Nitsch, R.M., Pruessmann, K.P., Hock, C., & Unschuld, P.G. (in submission). Regional Fluid-Attenuated Inversion Recovery (FLAIR) at 7 Tesla is associated with Amyloid beta load in hippocampus and brain-stem of cognitively normal elderly subjects.

- **Meier, I.B**, Gu, Y., Guzman, V.A., Wiegman, A.F., Schupf, N., Manly, J.J., Stern, Y., Luchsinger, J.A., Viswanathan, A., Martinez-Ramirez, S., Greenberg, S.M., Mayeux, R. & Brickman, A.M. (2014, February). Lobar microbleeds are associated with decline in executive functioning in older adults. *Journal of the International Neuropsychologial Society,* Seattle, WA.

- **Meier, I.B.**, Wiegman, A.F., Guzman, V.A., Provenzano, F.A., Manly, J.J., Schupf, N., Mayeux, R., & Brickman, A.M. (in press). Regional white matter hyperintensity volume and cognition predict death in a multi-ethnic, community cohort of older adults [abstract]. *Journal of the International Neuropsychological Society.* Paper (oral) presentation at the annual meeting of the International Neuropsychological Society, February 2013. Waikoloa, Hawaii.

- **Meier I.B.**, Grieve S.M., Korgaonkar M.S., Zimmerman M.E., & Brickman A.M. (2012, July). *Deciphering the cortical thickness signature: Biomarker for Alzheimer's disease or for memory?* Poster session presented at the Alzheimer's Association International Conference (AAIC), Vancouver, BC.

- **Meier I.B.**, Narkhede A., Provenzano F.A., Luchsinger J.A., Manly J.J., Willey J.Z., Viswanathan A., Martinez-Ramirez S., Greenberg S.M., and Brickman A.M. (2012, February). Lobar microbleeds, white matter hyperintensities, and memory in older adults. *Journal of the International Neuropsychological Society*, *18*, 224-225. Poster session presented at the International Neuropsychological Society, Montreal, QC.

- **Meier, I.B.**, Manly, J.J., Provenzano, F.A., Louie, K., Wasserman, B.T., Hector, J., Allocco, E., and Brickman, A.M. (2011, February). White matter predictors of cognitive functioning among older adults. *Journal of the International Neuropsychological Society*, *17*, 30-31. Paper (oral) session presented at the International Neuropsychological Society, Boston, MA.

- Brickman A.M., **Meier I.B.**, Korgaonkar M.S., Provenzano F.A., Grieve S.M., Siedlecki K.L., Wasserman B.T., Williams L.M., Zimmerman M.E. (2011, February). Testing the white matter retrogenesis hypothesis of cognitive aging. *Journal of the International Neuropsychological Society*, *17*, 52-53. Poster session presented at the International Neuropsychological Society, Boston, MA.